United States
Environmental Protection
Agency

FINAL DRAFT
ECAO-CIN-402
March, 1985
EPA-600/X-84-182-1

PB86-117819

Research and Development

DRINKING WATER CRITERIA DOCUMENT FOR LINDANE

Prepared for

OFFICE OF DRINKING WATER

Prepared by

Environmental Criteria and
Assessment Office
Cincinnati OH 45268

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TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

2.

3. RECIPIENT'S ACCESSION NO. PB86 117819/AS

SUBTITLE
Drinking Water Criteria Document for Lindane

5. REPORT DATE 3/85

6. PERFORMING ORGANIZATION CODE

HOR(S)
Environmental Protection Agency

8. PERFORMING ORGANIZATION REPORT NO.

PERFORMING ORGANIZATION NAME AND ADDRESS

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.

12. SPONSORING AGENCY NAME AND ADDRESS
U.S. Environmental Protection Agency
Office of Drinking Water (WH-550)
401 M St., S.W., Washington, D.C. 20460

13. TYPE OF REPORT AND PERIOD COVERED Scientific review

14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on lindane.

This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of lindane
- Toxicokinetics and human exposure to lindane
- Health Effects of lindane in humans and animals
- Mechanisms of toxicity of lindane
- Quantification of toxicological effects of lindane

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Lindane properties Lindane exposure Lindane toxicity Drinking Water		

18. DISTRIBUTION STATEMENT OPEN	**19. SECURITY CLASS** *(This Report)* Non-sensitive	**21. NO. OF PAGES** 195
	20. SECURITY CLASS *(This page)* Non-sensitive	**22. PRICE**

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DOCUMENT DEVELOPMENT

Cynthia Sonich-Mullin, M.S., Document Manager
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Helen H. Ball, M.S., Project Officer
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Authors

William Thompson
Franklin Research Center
Philadelphia, PA

Marvin Melzer, Ph.D.
Franklin Research Center
Philadelphia, PA

Scientific Reviewers

James D. Yarbourgh, Ph.D.
Mississippi State University

Harihara M. Mehendale, Ph.D.
University of Mississippi
Medical Center

Yogendra Patel, Ph.D.
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC

William Lappenbusch, Ph.D.
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC

Randall J.F. Bruins, M.S.
Environmental Criteria and
Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Frank Mink, Ph.D.
Environmental Criteria and
Assessment Office, Cincinnati
U.S. Environmental Protection Agency

William Bruce Peirano, M.S.
Environmental Criteria and
Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Jennifer Orme, M.S.
U.S. Environmental Protection Agency
Washington, DC

William E. Pepelko, Ph.D.
Carcinogen Assessment Group, OHEA
Washington, DC

Editorial Reviewers

Erma Durden, B.S.
Environmental Criteria and
Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Judith Olsen, B.S.
Environmental Criteria and
Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Document Preparation

Technical Support Services Staff: C. Cooper, P. Daunt, C. Fessler, K. Mann, B. Zwayer, Environmental Criteria and Assessment Office, Cincinnati

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CNS	Central nervous system
p,p'-DDE	p,p'-dichlorodiphenyldichloroethylene
dpm	Disintegrations per minute
DDT	Dichlorodiphenyltrichloroethane
FAO/WHO	Food and Agricultural Organization/World Health Organization
GABA	Gamma-aminobutyric acid
GI	Gastrointestinal
HCH	Hexachlorocyclohexane
γ-HCH	Lindane
t-HCH	Technical grade HCH
LD50	Median lethal dose
mIU	MilliInternational Unit
NADP	Nicotinamide-adenine dinucleotide phosphate
NADPH	Reduced NADP
ng	Nanogram
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
PTZ	Pentylenetetrazol
TDE	Dichlorodiphenyldichloroethane

METRIC CONVERSIONS

In this document, whenever an oral intake of lindane or any other HCH isomer is given in the literature in terms of ppm in the diet, the dietary ppm value is converted to its approximate dosage equivalent in terms of mg of toxicant/kg animal body weight by multiplication of the ppm value by the published diet fraction (food intake in kg/day/body weight in kg) of that particular species based on estimated food consumption. Conversion factors used were 0.05 for rats, 0.04 for dogs, 0.13 for mice and 0.028 for humans. Most feed data were converted in this manner; the exception being data from bird studies since the diet fraction for birds was not available.

I. SUMMARY

Lindane, the gamma isomer of hexachlorocyclohexane (HCH), is an organochlorine pesticide that is registered for use on livestock, pets and agricultural premises, and used for soil, foliar and seed treatment for a wide variety of food crops (NCI, 1977). Lindane is extracted from HCH by the use of selected solvents, most commonly methanol. Production of lindane in the United States reached a peak in the early 1950's and subsequently declined as the use of organophosphate insecticides increased (IARC, 1979); however, production of lindane was terminated in 1976 when Hooker Chemical Corporation ceased its operation (NRC, 1982).

Today lindane is primarily used for the control of various wood-inhabiting beetles, for seed treatment, and in pharmaceutical preparations (1% γ-HCH) as a scabicide and pediculocide. The annual use of lindane in the United States was ~1 million pounds during 1978 but has declined since then (NRC, 1982). In 1981, 123,350 kg (271,370 lbs) were imported into the United States (USITC, 1982).

When ingested by animals, lindane is readily absorbed from the GI tract into the bloodstream and is then distributed throughout the body. Turner and Shanks (1980) showed that in male Wistar rats ~48% of an oral dose of lindane appeared in the blood 30 minutes after administration. In female ICR mice ~40% of the administered dose was found in the whole carcass 20 minutes after treatment (Ahdaya et al., 1981). Lindane is also readily absorbed through the skin. When lindane cream (Kwell; 1% lindane) was topically administered to nine human adults, the plasma levels of lindane increased from undetectable levels at time zero to 10.3 ng/mℓ within 3 days (Hosler et al., 1979). Ginsburg et al. (1977) and Lange et al. (1981) demonstrated that in humans lindane was absorbed to a greater extent by damaged skin than by normal skin. Once absorbed, lindane preferentially accumulates in fatty tissue and the brain.

In humans, laboratory animals and *in vitro* systems using liver microsomes, lindane is metabolized under oxidizing conditions to pentachlorocyclohexene; tetrachloro-derivatives of 1-hydroxycyclohexene; isomers of mono-, di-, tetra- and pentachlorophenols; and mono-, di- and trichlorobenzenes. Most of these metabolites are excreted in the urine in free form or as conjugates of glutathione. In anaerobic soil systems, bacteria metabolize lindane to yield γ-pentachlorocyclohexene, α-HCH and γ-3,4,5,6-tetrachloro-1-cyclohexene.

The major toxic effects associated with lindane exposure in animals include suppression of the immune system, effects on the CNS (tremor, hyperexcitability and convulsions) and carcinogenesis.

Desi et al. (1978) described a dose-dependent immunosuppressive effect in rabbits treated with lindane and then challenged with *Salmonella typhi* vaccine. Dewan et al. (1980) reported similar results in albino rats fed lindane and challenged with *S. typhi* and *S. paratyphi* antigens.

Neurological manifestations of exposure to lindane have been reported in rats (Müller et al., 1981; Farkas et al., 1976), rabbits (Prasad, 1981), lambs (Harrison et al., 1980) and pigeons (Blakley, 1982). In these animals, lindane and other HCH isomers exhibited effects on nerve conduction and caused observable behavioral changes.

Numerous animal studies on the carcinogenic potential of lindane, other HCH isomers and t-HCH have been reported in the literature. Although some of the reports are contradictory, the preponderance of evidence indicates that lindane is carcinogenic in mice. Lindane has been found to be carcinogenic in ICR-JCL mice (Goto et al., 1972), CF_1 mice (Thorpe and Walker, 1973), dd mice (Hanada et al., 1973) and in $B6C3F_1$ male mice (NCI, 1977).

In humans, lindane exposure has been associated with neurotoxic effects, lower lymphocyte counts and reduced lymphocyte response to mitogenic stimulation. Several reports have also indicated that lindane causes aplastic anemia; however, the evidence is equivocal. There have been no reports documenting increased cancer risk in humans following exposure to lindane. On the contrary, several studies have failed to demonstrate any increased incidence of cancer in factory workers who were exposed to lindane for long periods of time. However, epidemiological studies are currently inadequate to establish the noncarcinogenicity of lindane in humans.

The toxic effects of lindane appear to be mediated by various activities at the level of the cell membrane. Lindane has also been shown to enhance the induction of mixed-function oxidases (MFOs).

The populations most at risk to lindane exposure are formulators and distributors, agricultural workers, and any other persons exposed to large amounts of lindane. Although the pharmaceutical applications of lindane are safe when used as directed, extreme caution should be exercised in the treatment of very young children because lindane is readily absorbed through the skin and can cause neurotoxic effects.

There are several areas in which evidence on the health effects of lindane is nonexistent, contradictory or equivocal. Further research is needed to provide additional information on the following:

- the association between lindane and aplastic anemia,
- the association between lindane and cancer in humans,
- the effects of lindane on the developing fetus and on neonates,
- carcinogenesis in species other than mice.

Both 1-day and 10-day health advisories (HA) were based upon a NOAEL of 12.3 mg lindane/kg bw fed to rats for 30 days. For adults the recommended 1- and 10-day HAs is 4.3 mg/ℓ and for children 1.2 mg/ℓ.

The recommended long-term acceptable daily intake (ADI) is equal to 0.023 mg/day. This value is based upon a NOAEL of 4 ppm dietary lindane given to rats for 84 consecutive days. Assuming a daily water intake of 2 ℓ/day, the adjusted ADI (AADI) is equal to 0.010 mg/ℓ.

Risk estimates for cancer were calculated based upon the oncongenic effects observed in the liver of mice fed lindane in the diet at 400 ppm. The estimated levels that would result in increased lifetime risks at 10^{-4}, 10^{-5} and 10^{-6}, respectively, by U.S. EPA (1980) and NAS (1977) are listed below.

	Associated Cancer Excess Lifetime Risk (μg/ℓ)		
	10^{-4}	10^{-5}	10^{-6}
U.S. EPA	2.650	0.265	0.0265
NAS	5.50	0.550	0.0550

II. GENERAL INFORMATION AND PROPERTIES

Introduction

Lindane (1α, 2α, 3β, 4α, 5α, 6β-hexachlorocyclohexane: γ-HCH) is the only one of eight stereoisomers of hexachlorocyclohexane (HCH) with effective insecticidal properties (Windholz, 1976). It is also used therapeutically as a scabicide, pediculicide and ectoparasiticide.

Other names for lindane include γ-benzene hexachloride (γ-BHC), γ-lindane, purified BHC, technical lindane, hexachlor, 666, hexachloran, benhexachlor, Viton, Gammexane, Gexane, Ben-Hex, Aphtiria, Aparasin, Streunex, Tri-6, Lindatox, Lorexane, Kwell, Quellada and Jacutin. In this document, HCH will be used as an abbreviation for hexachlorocyclohexane and the five commoner isomers will be identified by the appropriate Greek letters (α, β, γ, δ, ε). Lindane will be referred to as γ-HCH and technical grade HCH (composed of the five isomers) will be referred to as t-HCH.

Because of its persistence in the environment and continued use as an insecticide and scabicide, lindane has been evaluated in numerous studies for its effects on plant and animal (including human) life. This document will review up-to-date information on the properties of lindane, its occurrence in the environment, toxicokinetics, health effects on animals and humans, mechanisms of toxicity, risk assessment and will recommended maximum allowable contaminant levels.

Physical and Chemical Properties

Lindane and the other isomers of HCH differ in the spatial arrangement of the six chlorine atoms on the chair form of the cyclohexane ring (Figure II-1).

Physical and chemical properties of lindane are summarized in Table II-1. In addition, lindane is not reactive with strong acids; decomposes in the presence of alkali at ambient temperatures to form trichlorobenzenes; and decomposes in the presence of powdered iron, aluminum and zinc (Windholz, 1976). Lindane is very stable to the actions of heat, light and oxidation (Metcalf, 1981).

Production and Uses of Lindane

Lindane does not occur as a natural product (IARC, 1979). Lindane is extracted from HCH (produced by photochlorination of benzene) and then treated with nitric acid to remove odor. The crude product of benzene and sunlight contains 10-18% lindane. Pure lindane is obtained by treatment of the crude product with methyl alcohol or acetic acid (30-40% yield of γ-isomer) followed by fractional crystallization of the alcohol-soluble fraction from chloroform or chromatographic adsorption (Metcalf, 1981).

In the United States, commercial production of lindane was first reported in 1950 (U.S. Tariff Commission, 1951). The quantity produced/year peaked in the early 1950's and has since declined because of increased use of organophosphate insecticides. Since 1956, only one U.S. company, Hooker Chemicals and Plastics Corporation, has reported production of lindane; an estimated 227,000 kg were produced in 1972 (U.S. EPA, 1976a). Hooker discontinued production of lindane in 1976. Other countries producing lindane

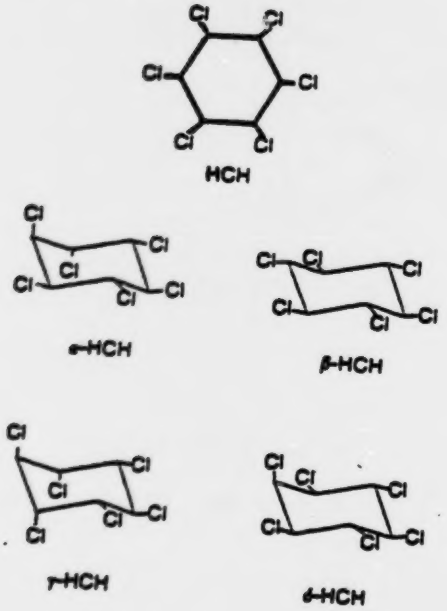
HCH
α-HCH
β-HCH
γ-HCH
δ-HCH

FIGURE II-1

Common Isomers of Hexachlorocyclohexane (HCH)

Source: Demozay and Marechal (1972)

TABLE II-1

Physical and Chemical Properties of Lindane

Property	Data	Reference
Molecular weight	290.85	Windholz, 1976
Appearance	white, monoclinic crystals	Demozay and Marechal, 1972; Grasselli and Ritchey, 1975; Hooker Chemical Corp., 1969
Melting point	112.5°C	Windholz, 1976
Boiling point	323.4°C	Demozay and Marechal, 1972; Grasselli and Ritchey, 1975; Hooker Chemical Corp., 1969
Odor	slightly musty	Windholz, 1976
Solubility in water at 25°C	7.3-7.9 mg/ℓ	Masterton and Lee, 1972; Kanazawa, 1981; Weil et al., 1974
Vapor pressure at 20°C	$(0.094-3.3) \times 10^{-4}$ torr	U.S. EPA, 1976a*
Density	1.85	Demozay and Marechal, 1972; Grasselli and Ritchey, 1975; Hooker Chemical Corp., 1969
Log octanol-water partition coefficient (log K_{ow})	3.61-3.72	Hansch and Leo, 1979; Kanazawa, 1981

*Some sources (i.e., Windholz, 1976) cite older measurements several orders of magnitude higher.

include France, West Germany, Spain, East Germany, Poland, Yugoslavia, Rumania, and the USSR (IARC, 1979). Imports of lindane in the United States totalled 123,350 kg in 1981 (USITC, 1982).

Lindane is available as emulsifiable concentrates, wettable powders, oil-base sprays, dusts, aerosol sprays, granules, and as a smoke generator (IARC, 1979). In the United States lindane is used primarily for seed treatment and to control various species of wood-inhabiting beetles. In 1974, the United States used ~270,000 kg lindane as an insecticide: 67% on livestock and poultry, 33% on crops (IARC, 1979). As of 1977, there were 557 Federal registrations for pesticide products containing lindane and 87 requests for Federal registrations for formerly state-registered products containing lindane (U.S. EPA, 1980). Data on the amounts of lindane currently used in the United States are not available.

Lindane is also used medically to treat scabies and lice on humans and ectoparasites on animals. For human use, lindane is available as a 1% lotion, cream, and shampoo. In 1974 <1000 kg lindane were used for medicinal purposes in the United States (Kastrup, 1976).

Sources in the Environment

Since lindane does not occur naturally, its presence in the environment results from its application as an insecticide and from spillage during transportation and storage (Kaphalia and Seth, 1981). Agricultural uses for pest control and the elimination of insect vectors are the main sources of lindane in the environment.

Pesticides can enter the atmosphere by volatilization from soil and water surfaces and from dust particles (Crosby, 1978). Soil obtains pesticides by way of direct application, rainfall, the movement of microorganisms, transport from plants, leaching, and the movement of subsurface water. Aquatic environments are contaminated by surface application, surface and subsurface runoff, and plant material.

Due to the persistence of lindane in the environment and its toxic effects, many industrialized countries have banned or restricted the use of lindane. However, because of its low cost, lindane in the form of t-HCH is still widely used in many developing countries. In the period 1977-1978, for example, India used a total of 28.64 million kg of t-HCH for agricultural and public health purposes (Aiyar, 1980).

Although there is a substantial amount of data on pesticide residues in various organisms, little information is available on the exposures that produced these residues.

Environmental Fate and Transport

As indicated earlier, lindane can enter the atmosphere in the form of spray pellets, granules or fumigants, or by volatilization from soil and water. Reports on the atmospheric transport of organic pesticides are sparse. In two recent studies, however, the researchers established the long-range atmospheric transport of organic pollutants to remote marine areas (Atlas and Giam, 1981; Tanabe et al., 1982).

Atlas and Giam (1981) measured the concentrations of organic pollutants, including γ-HCH, in the atmosphere and precipitation at Eniwetok Atoll in the North Pacific Ocean. This site was selected because of its remoteness from urban or manufacturing sources and because it was not subject to episodal or local contamination. A total of 17 atmospheric and 16 rain samples were analyzed and yielded mean γ-HCH concentrations of 0.015 ng/m³ and 0.51 ng/ℓ, respectively. Using the average rain and atmospheric concentrations, a washout factor of 34-38 was calculated for γ-HCH. From these data, the authors indicated that rainout and washout may be inefficient mechanisms for the removal of organic pollutants from the marine atmosphere and that vapor-phase deposition onto the sea surface may be the controlling factor for the transfer of some organic pollutants to the ocean.

In a study of the global distribution and atmospheric transport of chlorinated hydrocarbons, Tanabe et al. (1982) confirmed the widespread distribution of HCH isomers. HCH residues were detected in all air and water samples collected. In oceans bordering the Asian Continent (Western Pacific Ocean and Eastern Indian Ocean) the concentrations of HCH (sum of α, β and γ isomers) ranged from 1.1-2.0 ng/m³ in air and from 3.1-7.3 ng/ℓ in water, while in the Antarctic Ocean the HCH concentrations ranged from 0.09-0.17 ng/m³ in air and from 0.26-0.92 ng/ℓ in water. More α-HCH than γ-HCH was detected in the northern hemisphere, while γ-HCH was the dominant isomer in the southern hemisphere. The values detected reflect the major use of t-HCH in the northern hemisphere and the extensive use of γ-HCH in the southern hemisphere.

Volatilization of pesticides is a major factor for the occurrence of pesticides in the atmosphere over both rural and agricultural areas. Cohen and Pinkerton (1966) tracked the movement of a dust cloud from an agricultural area in west Texas to the Cincinnati, Ohio area where the atmosphere and rainfall were found to contain DDT and six other pesticides. In another study, Stanley et al. (1971) collected air samples at nine locations throughout the United States and analyzed them for 18 compounds. DDT and related substances were present in all samples while HCH isomers tended to occur over urban areas.

Under laboratory conditions, γ-HCH has been shown to undergo radiation- and photo-induced degradation (Hamada et al., 1981). Irradiation of crystalline γ-HCH with $4.8x10^6$ R of ^{60}Co γ-ray yielded α-HCH as the major product along with an isomer of pentachlorocyclohexane and δ-HCH. When γ-HCH in 2-propanol solution was irradiated for 15 minutes by ultraviolet produced by a 15 watt low pressure mercury lamp, the major decomposition compounds were two tetrachlorocyclohexene isomers (γ and ε) and two isomers of pentachlorocyclohexane. Similar transformations of lindane and other pesticides are thought to occur in the atmosphere.

The above studies show that atmospheric transport leads to the widespread dissemination of lindane and other pesticides in the environment and to the contamination of soil and water through rainfall in areas not directly exposed to pesticide application. In addition, the presence of light, water, reactive surfaces, oxygen and other oxidants are thought to result in pesticide transformation in the atmosphere.

In a review of the literature, El Beit et al. (1981a) states that the factors involved in the loss of pesticides from the soil are degradation, volatilization, leaching and adsorption. Pesticides may be decomposed by chemical, biological, or photochemical action. Chemical degradation involves conjugation, isomerization, reduction, dehydrochlorination, hydrolysis and oxidation. Little photodecomposition occurs in soil since radiant energy is not available, even near the soil surface. Volatilization has been shown to be a major factor in the reduction of pesticide residues in the soil. Volatility is affected by vapor pressure, molecular weight of the pesticide, soil organic matter, soil moisture, soil temperature and humidity of the air over the soil surface (Matsumura, 1975; Spencer et al., 1973; Igue et al., 1972). Adsorption and leachability of pesticides by the soil are influenced by solubility, texture of the soil, soil acidity, soil temperature, and molecular structure and hydrophobicity of the pesticide.

In soil, microorganisms are responsible for degradation of lindane. Combined dehydrochlorinations, dechlorinations and hydroxylations are important in the degradation of γ-HCH applied as at least 99% pure lindane for plant protection and pest control. Bacterial metabolism of lindane in flooded soil has been shown to produce γ-pentachlorocyclohexene, CO_2, γ-3,4,5,6-tetrachloro-1-cyclohexene, and α-HCH (Esaac and Matsumura, 1980). Lindane decomposition is retarded by molecular oxygen, nitrate, and manganese dioxide. In sterilized or distilled water, γ-HCH was relatively stable, while in natural water <30% of the applied dose remained after 16 weeks (Sharom et al., 1980). Various Clostridium species appear to be the most widespread γ-HCH decomposers, and are effective on γ-HCH, but not on the β- or α-isomers (Ohisa and Yamaguchi, 1979). Clostridium rectum degrades γ-HCH during the early growth phase but not during the resting stage (Ohisa and Yamaguchi, 1978). In order to degrade lindane, C. rectum requires leucine, alanine, pyruvate, a leucine-proline mixture, and molecular hydrogen (Ohisa et al., 1980). Maximum degradation activity by C. sphenoides on γ-HCH occurred at 40°C and pH 8 (Heritage and MacRae, 1979).

Haider (1979) demonstrated that Clostridia (a strict anaerobe) and Enterobacteriaceae and Bacillaceae (facultative anaerobes), all organisms known to evolve hydrogen during fermentation, were able to dechlorinate γ-HCH. During microbial degradation, organic-bound chlorine is released as a chloride; nearly chlorine-free, partly volatile metabolites are formed. Under submerged conditions, the half-life of γ-HCH was related to the number of cells of anaerobic γ-HCH decomposers (Ohisa and Yamaguchi, 1979).

A laboratory study of the sorption and desorption of α, β and γ-HCH isomers by 12 Indian rice soils differing widely in their physical and chemical characteristics was performed by Wahid and Sethunathan (1979). The soils showed marked differences in their ability to sorb HCH; sorption ranged from 40-96% for total HCH added and from 44-96% for γ-HCH. The most important factor governing the sorption and desorption of HCH was the organic matter content of the soils. Percent sorption increased dramatically with increasing soil organic matter content until an organic content of ~3-4% (corresponding to ~80% adsorption) was reached; thereafter, increases in organic matter only slightly increased adsorption. The importance of soil organic matter in the sorption of HCH isomers was also indicated by the drastic reduction in sorption capacity following treatment of the soil with H_2O_2: sorption of total HCH ranged from 5-46% and sorption of γ-HCH ranged from 6-38%. The sorption of γ-HCH was also significantly correlated with clay content and free iron oxide.

In another study, Wahid and Sethunathan (1980) examined the sorption-desorption of lindane by anaerobic and aerobic soils. Radiolabeled lindane (0.2 mℓ of acetone solution containing 0-1.5 μg lindane) was added to 30-day flooded soil (anaerobic system) and the system was equilibrated on a shaker for 30 minutes. Soils flooded just before the addition of lindane followed by a 30-minute equilibration served as controls. Soils produced by 30-day flooding sorbed less lindane than the aerobic soils. This difference was particularly marked in soils with low organic matter content. The decreased sorption of lindane by anaerobic soils low in organic matter content was attributed to a decrease in inorganic surface area caused by the prereduction of free iron oxides upon flooding. The prereduction of the soils by flooding had no effect on the desorption of lindane.

El Beit et al. (1981b) studied the effect of soil temperature, and the period of contact with soil on the leachability and adsorption of commonly used pesticides in two different soil samples. Gezira soil from the Sudan, packed in 30 cm x 2.5 cm glass columns, was treated with 100 μg pesticide/g soil and leached for long periods (>60 days). At temperatures between 2 and 25°C, γ-HCH experienced increasing losses through leaching (>50%) without attaining a constant level. At 45°C leaching was much lower (25%) and ceased after 40 days. Adsorption of γ-HCH also decreased progressively as the temperature increased. The reduction in adsorption at higher temperatures may be due to an increased rate of water movement through the soil and increased evaporation and degradation. In a sandy clay loam from England, the adsorption of all pesticides investigated decreased with time. The decreases were more pronounced at higher temperatures. It was speculated that the decrease in adsorption with time was due to microbial or chemical degradation or irreversible adsorption.

The movement and persistence of lindane in soil was demonstrated by Eidmann et al. (1979). Lindane-sprayed (1% active ingredient) seedlings of Norway spruce and Scots pine were transplanted to a mineral soil without humus and studied over a period of time for lindane residues. Only 2% of the original amount (15 mg/seedling) was present on the seedlings at the end of 1 year. In soil near the seedlings, lindane content increased rapidly during the first few weeks after planting. Lindane rapidly penetrated vertically in the soil; 2 weeks after planting an average of ~0.1 mg/kg was detected and maintained throughout the 1-year study period; at 1 year, ~2-3 mg lindane was found within a radius of 10 cm of the seedlings and down to 20 cm.

In plants, pesticides may undergo oxidation, reduction, hydrolysis or conjugation (Frear and Menn, 1978). Conjugation reactions are particularly important because conjugated metabolites are not excreted; instead they may be stored or incorporated into insoluble "terminal" residues and ultimately degraded in the environment or ingested by animals. Factors that may affect the behavior and fate of pesticides in plants include application methods, routes of absorption by the plant, interactions with other chemicals, growth and development, environmental stress, nutrition, disease and genetic variations.

In a comparison of the persistence, translocation and metabolism of six insecticides (DDT, lindane, fonophos, parathion, phorate and carbofuran) in two different soil types and oat plants grown in these soils, the insecticides were labeled with ^{14}C and extractable and unextractable ^{14}C residues were quantitated (Fuhremann and Lichtenstein, 1980). Only 0.7-4.3% of the applied lindane residues were taken up by loam-grown oats, while 4.6-12.6% were taken up by sand-grown oats. Most of the total radiolabeled plant residues of lindane were associated with the roots. Less than 1% of the soil-applied dose of lindane was translocated to the tops of the oat plants.

In a review of the literature, Crosby (1978) summarized the work of Mackay and Wolkoff (1973) and MacKay and Leinonen (1975) who studied the rate of evaporation of low-solubility contaminants from water bodies to the atmosphere and calculated the residence time of several pesticides, including lindane, in water in relation to vapor pressure, concentration, and other measurable properties. At 25°C lindane had a volatilization half-life of 191.25 days for water of 1 m depth.

When exposed to ultraviolet reduction in an atmosphere of nitrogen, γ-HCH rapidly disappeared from an aqueous solution: <1% of the original amount was left in solution after 30 hours of exposure (Malaiyandi et al., 1982). During the first 15 hours of the experiment the levels of the α-isomer increased rapidly while levels of the γ-isomer had dropped to ~10%. Thereafter the concentration of the α-isomer declined almost as fast as the γ-isomer. In the absence of nitrogen, almost 3 times as much time was necessary to reduce the concentration of lindane to <1%.

Malaiyandi et al. (1982) also studied the effect of ultraviolet light in the presence and absence of chlorine. Chlorine is commonly used in waste and potable water disinfection. It was shown that lindane degraded to some unknown, hexane-insoluble product(s), rather than isomerizing to the α-isomer, more readily in the presence than in the absence of chlorine. As the duration of exposure to ultraviolet irradiation and chlorine were increased simultaneously, the rate of loss of the γ-isomer was enhanced.

Shtannikov et al. (1977) demonstrated that chlorination of water containing lindane and other organochlorine compounds decreased the subsequent LD_{50} levels in mice and rats, presumably by conversion of these compounds to more toxic products.

Of six organochlorine pesticides studied (mexacarbate, parathion, toxaphene, DDT, dieldrin and lindane) γ-HCH was the least affected by photodegradation in the presence of algae (Matsumura and Esaac, 1979). Algal preparations (Anacystis nidulans and Microcystis aeruginosa), with or without a flavin cofactor, and 10 μℓ of 95% ethyl alcohol containing insecticide in 2.5-5 mℓ standard phosphate buffer were incubated anaerobically or aerobically and exposed to fluorescent light for 7-9 days at room temperature. When flavoproteins were present the photodegradation of all six pesticides was enhanced. These findings are significant since algae constitute the bulk of biomass in many aquatic systems and are known to collect pesticidal chemicals because of their large surface area.

Nitrogen-fixing, blue-green algae (*Nostoc muscorum* and *Wollea bharadwajae*), when repeatedly inoculated and removed from cultures, reduced the toxic effect of added γ-HCH (Kar and Singh, 1979). The pesticide was either accumulated or detoxified in the algal cells. Use of these algae for detoxifying polluted waters may be possible if the algae can be frequently removed.

In summation, lindane is present in the environment in soil, water, air and food, even in regions far removed from direct spraying. Once in the environment, lindane may be degraded, sorbed and desorbed, volatilized, excreted and leached. Factors affecting lindane's loss from the environment are its own chemical and physical properties, environmental conditions such as soil type, soil moisture, soil temperature and air humidity, and the presence of certain chemicals, bacteria and algae that aid in its degradation.

Bioconcentration

Szokolay et al. (1977) examined the relative cumulation of HCH isomers, including lindane and various components in the food chain in Czechoslovakia. Residues of lindane (in mg/kg) were as follows: in soil, ~0.005; in potatoes, ~0.01; in feed for laying hens, ~0.015; in eggs, ~0.008; in butter, ~0.04; and in human milk, 0.339. These observations indicate a more pronounced cumulation in animal products.

Table II-2 summarizes reported HCH residue levels in various animal tissues. Lower residues were found in tissues of animals feeding entirely on plant material (chickens, sheep, pigeons) while carnivores [vultures,

TABLE II-2

Reported HCH Residue Levels in Various Animal Tissues (mg/kg)

Animal (tissue)		Region	γ-HCH	Total HCH
Sheep[a]	(blood plasma)	Sprinagar, India	0.002-0.005	NS
	(skeletal muscle)		0.032-0.034	NS
	(body fat)		0.090-0.186	NS
Birds[b]				
Farm-bred chicken	(plasma)	Lucknow, India	0.002	0.008
	(brain)		0.002	0.016
	(depot fat)		0.092	0.253
Wild pigeon	(plasma)	Lucknow, India	0.016	0.048
	(brain)		0.021	0.355
House crow	(plasma)	Lucknow, India	0.013	0.035
	(brain)		0.014	0.248
	(depot fat)		6.982	22.487
Common pariah kite	(plasma)	Lucknow, India	0.119	0.064
	(brain)		0.013	0.119
	(depot fat)		3.921	6.567
Bengal vulture	(plasma)	Lucknow, India	0.068	0.112
	(brain)		0.335	1.247
	(depot fat)		11.966	13.980
Cattle egret	(plasma)	Lucknow, India	0.048	0.064
	(brain)		0.055	0.132
	(depot fat)		5.031	6.344
Birds[c]				
Seagulls	(plumage)	Italy	0-11.28	NS
	(fat)		0-0.91	NS
	(liver)		0-0.20	NS
Goats[d]	(muscle	Lucknow, India	0.005	0.018
	(brain)		0.010	0.068
	(liver)		0.009	0.032
	(body fat)		0.134	0.536
	(bone marrow)		0.063	0.203

TABLE II-2 (cont.)

Animal (tissue)		Region	γ-HCH	Total HCH
Buffalo[d]	(muscle)	Lucknow, India	0.004	0.012
	(brain)		0.012	0.076
	(liver)		0.012	0.038
	(body fat)		0.058	0.165
	(bone marrow)		0.121	0.252
Chicken[d]	(muscle)	Lucknow, India	0.017	0.109
	(brain)		0.027	0.162
	(liver)		0.049	0.195
	(body fat)		1.217	3.879
	(leg muscle)		0.007-0.037	0.034-0.243
	(breast muscle)		0.002-0.019	0.014-0.177
Buffalo[e]	(milk)	Lucknow, India	0.018	0.057
Goat[e]	(milk)	Lucknow, India	0.012	0.041
Gamebirds[f]	(muscle)	Tennessee, U.S.		
Grouse			0.99-2.17	NS
Quail			1.63-1.76	NS
Woodcock			1.63-1.83	NS

[a] Seth and Kaphalia, 1981

[b] Kaphalia et al., 1981

[c] Vannucchi et al., 1978

[d] Kaphalia and Seth, 1981

[e] Saxena and Siddiqui, 1982

[f] Blevins, 1979

NS = Not studied

cattle egret, kite (hawk)] had higher concentrations. However, the highest concentration of total HCH was found in depot fat of common house crows (omnivorous), perhaps because of ingestion of treated seeds and carrion of small animals that fed on treated seeds. In general, in the animals in which depot fat was tested, γ-HCH and total HCH accumulated to a much greater amount in the depot fat than in any of the other tissues. The exception to this was seagulls in which up to 11.28 mg/kg γ-HCH was accumulated in the plumage while only up to 0.91 mg/kg accumulated in the fat; plumage values for the other birds were not reported. In the Kaphalia and Seth (1981) study, residue values were reported for animals used for food. The residues in chickens in this study were much greater (1.217 and 3.879 mg/kg for γ-HCH and total HCH, respectively, in depot fat) compared with the Kaphalia et al. (1981) study (0.092 and 0.253 mg/kg, respectively). This difference is probably due to a different source of chickens. Gamebirds in the United States contained substantially more γ-HCH in their muscle than any of the other animals studied. Kaphalia et al. (1981) concluded that food habits and the food-chain concentration mechanism are more important in determining the total body burden of pesticide residues than age and size of the bird.

Farm animals may be exposed to pesticides through feed, air, water or through cutaneous application for protection from ectoparasites. However, only the oral and cutaneous routes are of practical importance (Talanov, 1978). Lipophilic pesticides such as lindane may accumulate in the adipose tissue since such pesticides are resistant to microorganisms in the alimentary tract and have poor water solubility. In the fat of cattle given controlled feed for 112 days before slaughter, Clark et al. (1974) found lindane levels 13 times higher in the adipose tissue (0.026 mg/kg) than in the feed (0.002 mg/kg). Similar experiments with broiler hens demonstrated 1.8 times more lindane in the animal fat that in the feed (Kan and Tuinstra, 1976).

Aquatic organisms bioconcentrate HCH isomers and lindane in their tissues to levels higher than the surrounding water concentration by a factor which is reported to vary from 35-617, depending on the organism and the tissue. In saltwater species, Schimmel et al. (1977) reported BCFs of 218 for soft tissue of American oyster, 130 for edible tissue of pinfish and 617 for offal tissue of pinfish, after exposure to 0.093 μg/ℓ t-HCH for 28 days. The relative percentages of the four HCH isomers in t-HCH (21% α-HCH, 39% γ-HCH, 2.1% β-HCH, 23% δ-HCH, and 14.9% unidentified) were similar to those in pinfish tissues (both offal and edible); no individual isomer was stored or purged selectively. Within 1 week of placement in HCH-free water, all detectable HCH was depurated in the pinfish and oysters.

Schimmel et al. (1977) also found that exposure for 4 days to lindane resulted in average BCFs of 63 for grass shrimp, 84 for pink shrimp, 490 for sheepshead minnow, and 218 for pinfish. Following exposure to t-HCH for 4 days, the average BCFs were 80 for pink shrimp and 482 for pinfish. The four isomers of HCH were bioconcentrated in tissues of pink shrimp and pinfish in approximately the same relative amounts as found in the HCH formulation. Canton et al. (1977) demonstrated that saltwater phytoplankton (Chlamydomonas and Dunaliella) rapidly accumulate and depurate HCH.

In a laboratory freshwater food chain [Chlorella sp. to Daphnia magna to Gasterosteus aculeatus (stickleback)], uptake of γ-HCH from water was rapid (67% applied was taken up within 24 hours), while uptake through the food chain occurred relatively slowly and depended upon the duration of the experiment (10-30 days) and the feeding rate. Rate of uptake from the water was influenced by the sex and physiological condition of the organisms, as demonstrated by males in the breeding condition accumulating 5.8 times as much lindane as normal males and females taking up more lindane than males (Hansen, 1980).

Freshwater BCFs have been reported from a small oligotrophic lentic ecosystem (a flooded limestone quarry), in which the fates of added lindane and DDE were followed for 1 year (Hamelink and Waybrant, 1976). Average steady-state BCFs for bluegills and for rainbow trout were 768 and 486, respectively. Mean concentration data from all thermal strata under summer water conditions were used in the calculations. Until fall turnover, 70% of the lindane remained evenly distributed throughout the epilimnion, the layer of water above the thermocline, and concentrations were relatively constant. Thereafter, the lindane concentrations were similar throughout the water column. Since the bluegill probably remained above the thermocline and thus was exposed to a higher concentration of lindane, the bioconcentration factor is likely to be less than the calculated value for this species. Macek et al. (1976) reported BCF values in laboratory exposures exceeding 250 days to be 35 for muscle tissue in bluegill, 70 for muscle tissue in brook trout, and 477 for eviscerated fathead minnows.

Humans accumulate lindane through the food chain, from ingestion of plants, water, animals and animal products, and milk. Residues of HCH have been found in human adipose tissue from India (mean 1.60 mg/kg) by Gupta et al. (1980) with higher concentrations in males (1.70 mg/kg) than females (1.21 mg/kg) and higher levels in persons older than 40 years (1.74 mg/kg) than younger persons (1.39-1.59 mg/kg). Median values for residues of HCH isomers in adipose tissue of persons from Czechoslovakia, determined by Szokolay et al. (1977), were as follows (in mg/kg): γ-HCH, 0.057; β-HCH, 0.208; δ-HCH, 0.011. When compared with residue levels in total diet, respective accumulation factors for these isomers were 11.4, 208.0 and 5.5. Levels of α-HCH were not determined.

Other studies of HCH residues in human adipose tissue reported values for β-HCH of 0.04-0.33 mg/kg in Mexicans (Albert et al., 1980), 1.23 mg/kg in Texans (Burns, 1974), 0.054 mg/kg in Canadians (Mes et al., 1977), 0.28 mg/kg in Britons (Abbott et al., 1968), 2.24 mg/kg in Italians (Paccagnella et al., 1967), and 1.39 mg/kg in Indians (Dale et al., 1965).

Higher levels of lindane (0.202 mg/kg) were found in human breast milk in India, where lindane continues to be used, compared with lower levels (from not detectable to 0.103 mg/kg) in women in countries where use of lindane has decreased in recent years (Saxena and Siddiqui, 1982).

In Canada, the mean residue level of lindane in milk fat was 0.047 mg/kg and for whole milk it was 0.002 mg/kg in 154 human milk samples (Dillon et al., 1981). Compared with a tolerance dose level of 0.2 mg/kg milk fat set by the Joint FAO/WHO Food Standards Programme, (FAO/WHO, 1974) only 3% of the samples exceeded that limit. In this study, a history of previous breast feeding was inversely correlated with γ-HCH levels.

In a study of 50 donors of breast milk in Hawaii, Takahashi et al. (1981) demonstrated HCH in 82% of the samples at a mean level of 0.086 mg/kg in milk fat. Age of the mother, previous nursing experience, weight of the mother, dietary habits of the mother, use of professional pest control preparations in the home, or occupational exposure of the spouse to pesticides had no significant effect on the levels of pesticides found in the milk samples.

In summation, γ-HCH, and other HCH isomers travel from organism to organism through the food chain. Such human exposure results from ingestion of plants, animals, animal products, milk and water containing these pesticides. As demonstrated in Table II-2, accumulation of lindane increases with progression along the food chain. Residues of lindane have been detected in all tissues tested in chickens, sheep, buffalo and gamebirds. Higher concentrations of lindane have been found in the fat of cattle and hens than in their feed, and in freshwater and saltwater organisms than in their prey or the water in which they live. Concentrations of residues in the adipose tissue of humans differ widely in the published literature; higher concentrations were found in countries and regions where lindane is still used extensively as a pesticide.

III. TOXICOKINETICS

Absorption

Animal Studies. Koransky et al. (1963) reported that intraperitoneal (i.p.) injection of rats with an oil solution containing 40 mg γ-HCH/kg bw resulted in 35% absorption. Ten percent of the lindane administered was still present in the abdominal cavity 24 hours after treatment. Low levels of lindane in the intestinal wall indicated a very rapid absorption process.

Turner and Shanks (1980) studied the absorption by the small intestine of some organochlorine compounds including lindane. Male Wistar rat intestinal loops were prepared and the intestinal lymphatic duct was cannulated at a point just before it entered the cisterna chyli. The loops were injected with 0.4 mℓ of a solution of lindane (0.05 or 0.1 μM) dissolved in rat bile. Control samples of mesenteric venous blood and lymph from the intestinal lymphatic duct were collected before administration of lindane. After lindane injection, the blood and lymph were sampled for 30 minutes. Of the injected lindane, 29.6-42.6% and 42.3-53.0% was absorbed from the intestine into the blood at the 0.05 and 0.1 μM levels, respectively. Blood/lymph ratios of lindane ranged from 151-2045 in rats treated with the 0.05 μM solution and from 1057-5296 in rats given the 0.1 μM solution. Thus, a considerable quantity of lindane can reach the blood from the GI tract, but only a small amount of lindane enters the lymphatic system from the intestine.

The study of Ahdaya et al. (1981) further reinforces the ready absorption of lindane into the GI tract. Radiolabeled lindane (1 mg/kg) in a

Emulphor:ethanol:water (1:1:8) carrier was administered by stomach needle into fasted (12 hours before lindane administration) female IRC mice. The mice were killed at intervals up to 60 minutes after administration. The appearance of radioactivity was used to estimate the amount of lindane absorbed by the GI tract (contents removed), liver, blood and remaining carcass. In the GI tract, radioactivity reached a maximum of 17% of the administered dose ~8 minutes after treatment. The amount of radioactivity subsequently fell to ~9% of the administered dose and remained at this level for the duration of the study. In liver, the level of radioactivity ranged from ~8% of the administered dose 15 minutes after treatment to ~5% at 60 minutes. The level of radioactivity in the blood remained nearly constant at 2% of the administered dose for the entire 60 minutes. Approximately 40% of the administered dose appeared in the carcass within 20 minutes of treatment and thereafter increased to 50% at 60 minutes. In the whole animal, the absorption of lindane reached a maximum of 70.7% of the administered dose 60 minutes after treatment.

Using squalene, a compound that is completely unabsorbed by rats as a positive control, Albro and Thomas (1974) estimated absorption of technical BHC at 95.8% within 4 days following single doses. Variations of dosage rates from 30-120 mg/kg had no influence on the proportion absorbed. The overall degree of absorption of technical BHC administered in food for 14 days was essentially identical (94.9%), but average absorption of the γ-isomer equalled 99.4% using radioactive BHC. Oshiba and Kawakita (1973) estimated that 85% of the γ-isomer was absorbed within 5 days.

The unusually high solubility of lindane in water, compared with other organochlorine pesticides, contributes to its rapid absorption and excretion. The rapidity of lindane absorption is also enhanced by lipid mediated carriers (Herbst and Bodenstein, 1972).

The relationship between solubility of lindane in the carrier and toxicity of the lindane preparation was demonstrated in the work of Muralidhara et al. (1979). When albino rats were fed lindane at a dose level of 125 mg/kg, the mortality observed was directly proportional to the solubility of the lindane in the particular carrier vehicle used to feed the lindane to the rats and the viscosity of the carrier. For example, the mortality was 70% when dissolved in groundnut (peanut) or coconut oils (in which lindane has a solubility of 15.1 g/100 g of carrier and viscosity of 60 and 48 centipoise units, respectively) while in castor oil (solubility, 7.07 g/100 g; viscosity, 465 centipoise units) there was no mortality. In water (solubility, 10 ppm; viscosity, 1 centipoise unit), mortality to a lindane dose of 125 mg/kg was 10%, while in olive oil (solubility, 10.25 g/100 g; viscosity, 66 centipoise units), the same lindane dose resulted in 20% mortality. Muralidhara et al. (1979) suggested that the reduced mortality in cases of low lindane solubility and high carrier viscosity may be due to the poor rate of hydrolysis and absorption in the small intestine resulting in quick elimination from the system.

Human Studies. Ginsburg et al. (1977) studied absorption of lindane in infants and children. Lindane was applied as a 1% lotion to the skin of 12 scabies-infected children and 8 uninfected children. Maximal levels of blood lindane (~0.028 μg/mℓ after an average administration of 129 and

158 µg of lindane in infected and uninfected subjects, respectively) were obtained within 6 hours; thereafter the level declined. Children with active infection and areas of damaged skin tended to have greater concentrations of lindane in the blood than did the siblings with normal skin.

In another study involving scabies patients, a 0.3% lindane emulsion was applied to the entire body of healthy adult volunteers and to adults with scabies (Lange et al., 1981). Initial serum values of lindane before treatment in normal subjects was 3 ng/mℓ (0.003 ppm) and ~40 ng/mℓ (0.04 ppm) in patients with scabies. Despite application of lindane to the entire body (3 times at 24-hour intervals), the maximal levels in healthy female volunteers, occurring ~4-6 hours after application, always dropped to similar values (~10 ng/mℓ) within 3-5 hours. In treated male patients with damaged skin, levels up to 425 ng/mℓ (0.425 ppm) were found compared with maximum values of 9.5 ng/mℓ (0.0095 ppm) in treated males with healthy skin.

Results obtained by Hosler et al. (1979) also showed ready absorption of topically administered lindane. After a single whole-body application of lindane cream (Kwell; 1% lindane), the plasma level found in nine adults (20-33 years old) rose from undetectable levels at time zero to a mean of 10.3±2.2 ng/mℓ within 3 days. Thus, it seems well established that when topically administered to humans, lindane is absorbed through the skin, reaching the blood where appreciable levels are achieved.

Accumulation/Distribution

Animal Studies. Extensive accumulation of lindane and other HCH isomers occurs in the milk of animals exposed to HCH compounds. Kapoor et al. (1980) reported high levels of γ-HCH (0.005-0.140 ppm) in the milk of water buffalo which grazed in areas treated with HCH in a malaria control program. The contamination of milk with γ-HCH was 7-10 times higher in HCH-sprayed localities than in DDT-sprayed areas where γ-HCH levels in milk ranged from 0.002-0.023 ppm.

After topical administration of Kwell (1% lindane in a cream consisting of stearic acid, lanolin, glycerol, 2-amino-2-methylpropanol, perfume and distilled water) to 12 newborn and 20 two-month-old guinea pigs, Solomon et al. (1977b) studied the accumulation of lindane into the blood and brain during a 3-day period. Each group of guinea pigs (newborn and 2-month-old) was divided into three subgroups (A, B and C). Animals in Group A received a single topical application of 20 mg Kwell and were sacrificed 24 hours later. Animals in Groups B and C received the initial application of Kwell followed by another application (20 mg) at 24 hours. Group B animals were then killed while Group C animals received a third 20 mg application of Kwell 48 hours after the initial application. Group C animals were killed 72 hours after the initial application. In the newborn guinea pigs, the mean levels of lindane in the blood were 0.4[illegible]0.2 μg/mℓ in Group A, 0.47±0.2 μg/mℓ in Group B, and 0.81±0.2 μg/mℓ in Group C. In the 2-month-old animals the mean blood levels were 0.12±0.1, 0.26±0.2 and 0.57±0.3 μg/mℓ, respectively, for Groups A, B and C. In brain tissue, Groups A, B and C had lindane levels of 4.5±0.5, 12.4±6.8 and 15.6±13.0 mg/kg, respectively, in the newborn guinea pigs, and 2.6±2.5, 6.4±8.2 and

8.3±3.5 mg/kg, respectively, in the 2-month-old animals. Lindane was not detected in the blood or brain of untreated controls.

Koransky et al. (1963) reported that radioactivity appeared very quickly in the fatty tissue of rats following i.p. administration of ^{14}C labeled γ-HCH (14 mg/kg bw). At least 75% of the labeled γ-HCH was consistently found in the skin, muscle and fatty tissue. Nakajima et al. (1970) showed that ^{14}C labeled HCH isomers were uniformily distributed in the adipose tissue throughout the body of mice.

HCH (exact isomer not specified) in groundnut (peanut) oil was fed at 2.5 mg/kg bw (50 ppm in the diet) to albino rats for a period of 3 months by Chand and Ramachandran (1980). At the end of the feeding experiment, HCH accumulation was determined to be 0.08 mg/ℓ in serum, 0.334 mg/kg in liver and 1.29 mg/kg in body fat of HCH-fed rats compared with levels in control rats (fed diet containing groundnut oil only) of 0.013, 0.032 and 0.94, respectively. Thus, HCH was preferentially accumulated in the fatty tissues.

The relationship between water solubility of various organic compounds (including insecticides such as HCH) and their accumulation in fatty tissue was reviewed by Geyer et al. (1980), who found that greater water solubility was correlated with reduced accumulation of the insecticide in the fatty tissue of the rat. Lindane, with a water solubility of 7.3-7.8 mg/ℓ, has a BCF (μg/g fatty tissue/μg/g of the chemical in the diet) of 0.4-1.4. This compares, for example, with p,p'-DDE, water solubility 14 μg/ℓ and a BCF of 10.3, and hexachlorobenzene, solubility 5 μg/ℓ and a BCF of 9.4-13.6.

Male weanling rats were fed one of three nutritionally adequate diets with or without 0.14 mg/kg bw (2.80 ppm) of a mixture of six organochlorine insecticides [DDT, TDE, DDE, lindane 0.007 mg/kg bw (0.14 ppm), dieldrin and perthane] until they reached 250 days of age. From day 251 to day 300, half of the rats in each group were restricted to 50% of their food intake. The accumulation of each insecticide was determined in adipose tissue, liver and brain (Lakshmanan et al., 1979). In adipose tissue, lindane concentrations were low ($\leq$0.2 mg/kg) and differences because of diet and age were not significant. The total amount of lindane in adipose tissue, however, was significantly reduced with dietary restriction from 8 to 4 µg in rats fed the high-fat diet; from 5 to 2 µg in rats fed low-fat diet 1 (LF-PB-BS); and from 6 to 3 µg in rats fed low-fat diet 2 (LF-BS-CO). Lindane was rarely detected in the liver, and when present was at a concentration of <0.05 mg/kg. In the brain, lindane was found in amounts ranging from 0.02-0.04 µg/kg. Diet and treatment had no significant effect on lindane content of the brain.

Bergman et al. (1981) used a whole-body autoradiographic technique to study the distribution patterns of chlorinated xenobiotics in the mouse brain. An intravenous (i.v.) dose of 5.2 µmole lindane/kg was found to be evenly distributed in the brain.

Chadwick et al. (1978a) reported that weanling female Sprague-Dawley rats fed high fiber laboratory chow (Purina brand) retained a significantly greater amount of radioactive label (following oral administration of 2.87 mg ^{14}C-labeled lindane) than did rats fed a low fiber diet. Significant differences were found in the brain, liver, kidney, stomach and muscle.

Data on the effect of diet on the retention of ^{14}C-lindane are presented in Table III-1. The organ weights of animals fed the high fiber chow diet were also greater than those fed a low fiber diet.

Accumulation studies have been conducted in various species of birds. Blevins (1979) reported that lindane accumulated in various game birds found in Tennessee (adult grouse, woodcock, quail) in amounts ranging from 0.99-2.17 mg/kg of muscle tissue. This exceeded the FAO/WHO (1974) residue tolerance limit of 0.1-0.5 mg/kg/day. A study by Kan (1978) showed that β-HCH accumulates in poultry to a much greater extent than does α-HCH or lindane. In terms of level in the fat/level in the diet, the following ratios were observed: α- and γ-HCH (lindane), 1.8, β-HCH, 18. Thus, there is extensive accumulation of lindane and its isomers in birds that indicates that humans might be exposed to lindane not only from direct contact with the compound but also by way of eating birds.

Human Studies. HCH accumulation in the serum of occupationally-exposed Yugoslavian workers was markedly increased when compared with the general population (Krauthacker et al., 1980). The mean serum lindane concentration in the Continental north (urban, northern part of the country) general population was 3.1 µg/ℓ compared with 10.4 µg/ℓ in exposed workers; in the Continental south (urban, southern part of the country) areas, these values were 3.8 and 26 µg/ℓ, respectively.

Accumulations of γ-HCH (lindane) were determined in the blood of people living in the Love Canal area of New York State. The Health Effects Research Laboratory of the U.S. EPA (Bristol, 1980) reported that 21% of 33

TABLE III-1

Effect of Diet on Retention of Radioactivity Following ^{14}C-Lindane Treatment[a]

Organ	LRD[b]	LRD+[b]	PLC[b]
Brain[c]	0.40 ± 0.07	0.56 ± 0.06	0.07 ± 0.05[f]
Liver[c]	3.86 ± 1.34	6.82 ± 0.98	7.96 ± 0.89[f]
Kidney[d]	0.83 ± 0.18	1.20 ± 0.21	1.58 ± 0.15[f]
Stomach[c]	1.03 ± 0.25	2.36 ± 0.77	4.57 ± 1.16[f]
Large Intestine[c]	7.62 ± 1.05	12.90 ± 2.65	8.88 ± 0.98[f]
Muscle[e]	0.22 ± 0.04	0.39 ± 0.06	0.50 ± 0.07[f]

[a] Source: Chadwick et al., 1978a

[b] LRD = Low Residue Diet; LRD+ = Low Residue Diet plus 10% pectin; PLC = Purina Lab Chow.

[c] Expressed as dpm x 10^{-4}/whole organ

[d] Expressed as dpm x 10^{-4}/pair of kidneys

[e] Expressed as dpm x 10^{-4}/g tissue

[f] Values differ significantly from LRD values: $p<0.05$

subjects examined had blood levels of 0.1-0.6 ng/g (ppb) of lindane (mean value = 0.2 ppb). None of these people had any detectable amount of α-HCH in their blood.

Gupta et al. (1982) studied the residues of HCH in human serum after a 16-week exposure to t-HCH under field conditions (spraying to control malaria). t-HCH was used as a 50% water dispersible powder providing a 1% suspension of γ-HCH in water. With the aid of a stirrup pump, 20 mg/square foot of the solution was applied. A total of 248 men were distributed into five groups: Group 0 (previously unexposed) 32 men; Group I (exposed 1 season) 27 men; Group II (exposed 2 seasons) 81 men; Group III (exposed 3 seasons) 68 men; and Group IV (exposed more than 3 seasons) 40 men. Before the 16-week exposure, mean serum γ-HCH levels in Groups 0, I, II, III and IV were 0.009±0.0128, 0.004±0.0074, 0.006±0.0092, 0.009±0.0120, and 0.008±0.0099 mg/ℓ (ppm), respectively. After exposure the following serum γ-HCH levels were found: 0.037±0.0322 mg/ℓ in Group 0; 0.037±0.0326 mg/ℓ in Group I; 0.028±0.0214 mg/ℓ in Group II; 0.034±0.0349 mg/ℓ in Group III, and 0.025±0.0168 mg/ℓ in Group IV.

An additional study of accumulation of HCH isomers (including lindane) was reported by Baumann et al. (1980). Occupationally-exposed control subjects (clerical workers not exposed to HCH isomers) showed virtually no HCH isomer accumulation in their sera. On the other hand, production workers who were exposed to these agents showed the following range of serum values (μg/ℓ) for the various isomers: α-HCH, 10-273; β-HCH, 17-760; and γ-HCH (lindane), 5-188. The accumulation in adipose tissue was 0.01-0.2, 0.3-2.4 and 0-0.1 mg/kg extractable lipids, respectively. Accumulation of the β-HCH isomer increased approximately linearly with time of exposure.

Lindane has also been shown to enter the fetus through the placenta. Poradovsky et al. (1977) found residues of lindane in the fatty tissue of pregnant women and in the vernix caseosa of their newborn babies. In a study of 25 pregnant Indian women not occupationally-exposed to pesticides, Siddiqui et al. (1981b) found that 5 times more γ-HCH accumulated in the milk [40 ng/ℓ (0.040 ppm)] than in the maternal blood [7.5 ng/ℓ (0.0075 ppm)]. Umbilical cord blood contained 5.6 ng/ℓ (0.0056 ppm) lindane. The study showed that lindane accumulates in the mother and can be transferred to the neonates through the milk and to the fetus through the placenta. No difference was found with regard to HCH accumulation related to dietary habits, geographic location, age or social status of the mothers in this study.

In another study of 100 women reported by Saxena et al. (1981), differences were noted in the accumulation of lindane in the maternal blood of pregnant women based on the age and residence of the women. In comparing 60 women aged 18-25 with 40 women aged 26-34 years, the older women showed more lindane in the maternal blood (0.0274±0.0288 mg/ℓ) than the younger women (0.0147±0.0192 mg/ℓ). This suggests that the longer the potential exposure to lindane, the higher the accumulation of the lindane in the maternal blood system. The older women also had higher lindane levels, compared with the younger women, in the placenta (0.0236±0.0214 mg/kg vs. 0.0129±0.0077 mg/kg) and umbilical cord blood (0.0149±0.0063 mg/ℓ vs. 0.0102±0.0161 mg/ℓ). Rural women had a higher accumulation (0.0184±0.0229 mg/ℓ) of lindane in the maternal blood system than women living in urban areas (0.0122±0.0252 mg/ℓ). Placental concentrations of lindane in urban women (0.0189±0.0176 mg/kg) did not differ significantly from those in rural women

(0.0175±0.0169 mg/kg) while concentrations in umbilical cord blood were significantly different when these two groups were compared (0.0169±0.0277 mg/ℓ in urban women and 0.0088±0.0096 mg/ℓ in rural women).

Siddiqui et al. (1981a) demonstrated the accumulation of γ-HCH in the fatty tissues of 50 Indian males (10-60 years old) at autopsy. The mean concentration of γ-HCH in adipose tissue was 1.230 mg/kg with a range of 0.721-3.012 mg/kg. Analysis of the data with respect to age (length of exposure) showed the highest concentration of lindane in the 26 to 40-year age group (1.50±0.28 mg/kg) followed by the 41 to 60-year age group (1.15±0.25 mg/kg) and the 10 to 25-year age group (1.00±0.22 mg/kg). The mean concentrations of γ-HCH were also higher in nonvegetarians (1.35±0.26 mg/kg) compared with vegetarians (1.07±0.22 mg/kg). The concentrations in urban and rural residents were 1.22±0.24 and 1.24±0.24 mg/kg, respectively.

Accumulation of lindane varies with the race of the human exposed. In a study of the effects of racial stratification in the contiguous United States on accumulation of lindane (and other organochlorine insecticides) by Kutz et al. (1977), it was found that Negroes would accumulate about twice as much lindane in their adipose tissue as did Caucasians.

Szymczynski and Waliszewski (1981a) collected semen samples from a random population of 50 patients undergoing evaluation of fertilization ability and analyzed the samples for residues of chlorinated pesticides and their metabolites by gas-liquid chromatography (GLC). The values of HCH isomers ranged from 0.001-0.30 µg/g semen. The highest absolute value of an HCH isomer was found for ε-HCH. This finding is noteworthy in that t-HCH containing α-, β-, δ- and ε-HCH had been banned in Poland 12 years prior to this study. Only γ-HCH had been used up to the time of the study. Of the samples studied, 70% were positive for γ-HCH (0.003 μg/g), 62% for α-HCH (0.002 μg/g), 8% for β-HCH (0.003 μg/g), 72% for δ-HCH (0.004 μg/g), and 62% for ε-HCH (0.005 μg/g). It was suggested that the higher levels of δ- and ε-HCH in the semen may be indicative of increased excretion of these isomers by the male reproductive tract.

When accumulation of HCH isomers was compared in three types of tissues, Szymczynski and Waliszewski (1981b) found that there was very little accumulation of lindane in the semen (0.003 μg/g) and testicles (0.009 μg/g) of the human compared with that in fatty tissue (0.018 μg/g). All HCH isomers were detected in semen, only α- and γ-HCH were detected in testicles, and β-, γ- and δ-HCH were detected in fatty tissues.

These studies indicate that much of the lindane that enters the human body accumulates in the fatty tissue, with considerable amounts also accumulating in mother's milk. The human results therefore correlate well with the animal models. No study of accumulation of lindane in the human brain has as yet been reported.

Metabolism

One report established that lindane isomerizes to the α-isomer but not to the β-isomer on incubation with reduced hematin (Saleh, 1980). The study did not evaluate the significance of the isomerization under metabolic or environmental conditions.

Animal Studies. Engst et al. (1976) reported the presence of di-, tri- and tetrachlorophenols and 2,3,4,5,6-pentachloro-2-cyclohexen-1-ol in the blood, liver, kidneys, spleen, heart and brain of rats fed γ-HCH. These metabolites were not detected in the intestine or feces. A pathway for the metabolism of γ-HCH was presented by Chadwick et al. (1975), demonstrating that γ-HCH was metabolized to an intermediate hexachlorocyclohexene that underwent subsequent degradation to yield 2,3,4,5,6-pentachloro-2-cyclohexen-1-ol, two tetrachlorophenols, and three trichlorophenols. Freal and Chadwick (1973) showed that the metabolism of γ-HCH was enhanced by pretreatment with other HCH isomers. Noack et al. (1975) demonstrated that preapplication of γ-HCH was able to stimulate its own biodegradation in rats.

Kujawa et al. (1977) administered lindane orally to rats (8 mg/kg bw) after which they studied the nature of the metabolites in urine, liver and blood. The major products found in urine were pentachlorophenol, 2,3,4,6- and 2,3,5,6- tetrachlorophenol, and 2,4,6-trichlorophenol. Metabolites in the blood were the same as those found in urine. In the liver, 2,3,4,5,6-pentachlorobenzene and γ-pentachlorocyclohexene were found in addition to the tetrachlorophenols. The kidneys contained considerably higher levels of the γ-pentachlorocyclohexene than did the liver. γ-Pentachlorocyclohexene was also detectable in the spleen, heart and brain. No metabolites were found in the adrenals. In a study of lindane metabolism by rats, Engst et al. (1979) found that the half-life of ^{14}C-labeled lindane was 3-5 days. The main metabolites were tri- and pentachlorophenol, and two tetrachlorophenols. 2,3,4,5,6-Pentachlorocyclohexene was found in liver, kidney and other organs.

In an *in vivo* study in female Sprague-Dawley rats fed diets containing lindane, Chadwick et al. (1978b) reported the formation of three additional lindane metabolites. Two configurational isomers of 2,4,5,6- and 2,3,4,6-tetrachloro-2-cyclohexen-1-ol were identified in rat urine, and γ-3,4,5,6-tetrachlorocyclohex-1-ene was found when liver preparations were incubated in the presence of an NADPH-generating system and nitrogen was gently bubbled into the incubation flask.

That some of these metabolic steps may involve oxidative processes was shown by *in vitro* studies conducted with subcellular fractions of animal cells. In a study using male and female Wistar rats, Tanaka et al. (1979) isolated liver microsomes and incubated them with lindane in the presence of oxygen and a source of NADPH. Gas chromatographic analysis revealed that the major product was the 2,4,6-trichlorophenol. In a study involving the use of the soluble fraction of chicken liver cells, Foster and Saha (1978) found that this cell fraction contains a glutathione-dependent set of dehydrochlorinase enzymes that metabolize the α-, γ- and δ- (but not the β-) HCH to the following major metabolites (amounting to 66% of the original HCH administered): all stereoisomers of dichlorobenzene; 1,2,3- and 1,2,4-trichlorobenzene; and the pentachlorocyclohexene. The formation of these products reflects the occurrence of a dehydrochlorination reaction. Substitution of a hydroxyl group for chlorine on the six-membered ring was indicated by the formation of dichlorophenols and trichlorophenols, which also reflect extensive dehydrochlorination, possibly by reaction with the dehydrochlorinase enzymes postulated by Foster and Saha (1978) to be present in the supernatant fraction of these cells. Minor metabolites identified included chlorobenzene and two isomers of trichlorocyclohexene.

Macholz et al. (1982a) reported that the major metabolites formed in male Wistar rats given α-HCH orally (3000 and 600 ppm of feed for 30 days) included all isomers of trichlorophenol and the tetrachlorophenol, all of which were excreted in the urine. Another metabolite, not excreted in urine, was the pentachlorocyclohexene. Similar metabolites were found after feeding of rats with the same amount of the β-isomer of HCH (Macholz et al., 1982b).

The metabolism of lindane appears to vary with the genetic strain of the animal studied. Liu (1982) studied the metabolism of lindane in two strains of mice, the C57Bl/6 (or B6) strain and the DBA/2 (or D2) strain. In both strains, a single short-term dose of lindane gave rise primarily to the 2,4,6-trichlorophenol and more slowly to the 2,3,4,6-tetrachlorophenol. Long-term lindane administration resulted in greater toxicity in D2 mice than in B6 mice. The increased toxicity was associated with higher terminal blood and brain lindane concentrations in D2 than in B6 mice. Furthermore, daily blood levels of 2,4,6-trichlorophenol and 2,3,4,6-tetrachlorophenol were lower in D2 mice than B6 mice. With continued administration of lindane, however, the levels of 2,3,4,6-tetrachlorophenol in the D2 mice increased to above those in the B6 mice. D2 mice exhibited more 2,4,6-trichlorophenol in the liver, kidney and spleen than did the less susceptible B6 mice.

Gopalaswamy et al. (1980) in an in vitro study using rat liver slices found that lindane was converted to the following products: pento- and trichlorophenols and, in addition, hexachlorobenzene. The researchers suggested that in assessing the toxicity of lindane, the toxicity of hexachlorobenzene must also be considered.

The presence of other agents has been shown to affect the metabolism of lindane. Chadwick et al. (1978c) treated male Wistar rats with cadmium (0-3.20 ng/kg) by i.v. injection followed by 1.83 mg lindane orally 24 hours before sacrifice at 3 days, 1, 2, 3 or 5 weeks after the initial cadmium injection. Significant inhibition of the hydroxylation of 1,3,5- and 1,2,4-trichlorobenzene and 1,2,3,5- and 1,2,3,4-tetrachlorobenzene was observed 3 days after cadmium administration. One week after cadmium administration, no significant inhibition of hydroxylation was observed. However, at later times (2-5 weeks after cadmium administration), significant inhibition was again observed. A significant cadmium-induced decrease in the excretion of lindane metabolites was observed at 3 days, followed by apparent recovery to control levels at 1 and 2 weeks, then recurrence of significantly reduced levels 3-5 weeks after treatment began. These effects of cadmium on lindane metabolism may have resulted from the direct or indirect action of cadmium on hepatic microsomal enzymes; the recurrence of impairment 3-5 weeks after treatment may have been due to secondary effects of cadmium on the metabolism and disposition of copper and zinc (Chadwick et al., 1978c).

Chadwick et al. (1981) fed female Sprague-Dawley rats diets containing either Arochlor 1254 [25 mg/kg bw (500 ppm)], phenobarbital [17.8 mg/kg bw (356 ppm)] or β-naphthoflavone [20.9 mg/kg bw (418 ppm)] for 1 week and then administered 1.89 mg lindane orally. After the rats were sacrificed 24 hours later, lindane metabolism, and excretion and distribution of metabolites were studied. Each of the MFO inducers affected metabolism of lindane: body weight decreased in rats treated with Arochlor 1254 and increased in those given phenobarbital and naphthoflavone; excretion of the administered dose in the urine, feces and expired air increased from a control value of 22% to 82% with Arochlor and 78% with phenobarbital but was not affected by naphthoflavone; excretion of neutral metabolites increased with phenobarbital and Arochlor; all three MFO inhibitors resulted in decreases in the formation of conjugated sulfates and increases in the formation of conjugated glucuronides.

Human Studies. Metabolism of lindane (and other HCH isomers) in humans seems to entail extensive dehydrochlorination (to form cyclohexene derivatives) and the formation of various chlorinated phenols, by way of either oxidative or nonoxidative pathways. Fitzloff et al. (1982) found that human liver microsomes converted lindane to various metabolites, one product being hexachlorocyclohexene (a product whose formation might imply an oxidative process operating in these human microsomes on lindane causing loss of saturation of the cyclohexane ring). Other products were 1,3,4,5,6-pentachlorocyclohexene, 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol and pentachlorobenzene (another product whose formation might suggest an oxidative process in the metabolism of lindane by humans). Engst et al. (1979) found that lindane was metabolized to tri- and pentachlorophenols when inhaled by humans.

Excretion

Animal Studies. An equilibrium concentration and stabilization will be reached following continual administration of γ-HCH to an organism. The self-induced, rapid biological deterioration of γ-HCH minimizes the health hazards associated with its use (Sieper, 1972, Chadwick et al., 1971; Chadwick and Freal, 1972). Even after prolonged administration, γ-HCH is completely eliminated from the body after application is terminated.

Frawley and Fitzhugh (1949) demonstrated that, in rat fatty tissue, a γ-HCH concentration of 102 mg/kg (102 ppm) dropped to zero 1 week after administration of γ-HCH was discontinued. Lehman (1952a,b) demonstrated that a concentration of 281 mg/kg (281 ppm) in the fatty tissue was completely eliminated within 2 weeks. Kitamura et al. (1970) fed rats a diet containing 10 mg/kg of γ-HCH over a 20-day period. One day after return to a normal diet, no residue could be detected in the body.

Very little γ-HCH is excreted unaltered. Laug (1948) detected only about 4% γ-HCH in the urine of rats fed γ-HCH in the diet (dosage unspecified). No reports of unaltered γ-HCH excretion following i.p. injection have been found.

Excretion of lindane in exhaled air and in urine was studied in fasted mice given a dose of 1 mg/kg bw by intubation (Ahdaya et al., 1981). Only a trace of lindane was excreted through the lungs (i.e., as carbon dioxide), while the urine contained 4.1% of the administered lindane after 60 minutes.

Stein et al. (1980) studied the elimination of γ-HCH from depot fat, skeletal muscle, brain and blood in male and female Wistar rats. Following i.p. administration of 10 mg/kg lindane or lindane-d_6 (perdeuterated lindane) the influence of sex or perdeuteration on the elimination of lindane from rat tissue was determined. The results of this experiment are presented in Table III-2. Considerable elimination from depot fat, brain and muscle (by ~50-75% of the original lindane levels) was observed 2-4 days after treatment with lindane. In depot fat, the half-time for elimination of lindane was 1-2 days in male and female rats and 2.1 days in male rats

TABLE III-2

Effect of Sex and Perdeuteration on Elimination of Lindane from Wistar Rats[a]

Tissue[b]	Days After Application	Lindane (males)	Lindane (females)	Lindane-d_6 (males)
Depot fat	1	42.3 ± 10.6	38.1 ± 10.6	110.0 ± 33.0
	2	20.9 ± 3.4	ND	72.4 ± 16.2
	4	9.6 ± 2.2	15.3 ± 2.0	39.7 ± 8.2
	7	ND	2.0 ± 1.6	ND
	8	0.6 ± 0.3	ND	ND
	14	0.06 ± 0.02	0.14 ± 0.05	ND
Brain	1	1.1 ± 0.2	1.9 ± 0.2	2.8 ± 0.42
	2	0.3 ± 0.1	ND	2.0 ± 0.26
	4	0.15 ± 0.02	0.37 ± 0.09	1.0 ± 0.1
	7	ND	0.06 ± 0.04	ND
	8	0.01 ± 0.005	ND	ND
	14	<0.005	0.01 ± 0.002	ND
Skeletal Muscle	1	0.7 ± 0.1	ND	1.6 ± 0.25
	2	0.2 ± 0.05	ND	1.2 ± 0.08
	4	0.1 ± 0.05	ND	0.7 ± 0.08
	8	0.01 ± 0.001	ND	ND
	14	<0.005	ND	ND
Blood	1	0.2 ± 0.03	ND	ND
	2	0.07 ± 0.04	ND	ND
	4	0.04 ± 0.02	ND	ND
	8	<0.01	ND	ND
	14	<0.01	ND	ND

[a] Source: Stein et al., 1980

[b] All values represent the tissue content of lindane in μg/g wet weight.

ND = Not determined

given lindane-d_6. Stein et al. (1980) also monitored the intestinal excretion of lindane or lindane-d_6 given i.p. (10 mg/kg) to male rats. Over a 4-day period, 1.3±0.4% of the lindane administered and 7.2±1.3% of the lindane-d_6 administered were recovered in the feces. Stein et al. (1980) concluded that intestinal excretion of unaltered compound could not explain the rapid elimination of lindane-d_6.

The urinary products of lindane were studied in male Wistar rats (Kurihara et al., 1979). Various phenylmercapturic acid derivatives were observed, formed by reaction of lindane metabolites (formed in the endoplasmic reticula of cells where dechlorinations and dehydrochlorinations occur) with glutathione. Reaction of these lindane metabolites with glutathione occurs in the cytosol of cells. The following chlorinated phenylmercapturic acids were observed in urine: 4-chloro-, 2,4- and 3,4-dichloro-, and 2,3,5- and 2,4,5-trichloro-phenylmercapturic acids. A sample pathway can be presented as follows: lindane loses one molecule of HCl to yield the pentachlorocyclohexene. This reacts with glutathione to yield the glutathione substituted tetrachlorocyclohexene (glutathione substituting for one of the chlorine atoms). This product loses two molecules of HCl to yield 2,4-dichlorophenylmercapturic acid, which is one of the lindane products found in urine (Kurihara et al., 1979). According to Portig et al. (1979) β-HCH seems to resist, to some extent, conversion to the glutathione derivatives while lindane and the α-HCH, as well as their pentachlorocyclohexene metabolites are converted to glutathione conjugates by way of a transferase enzyme present in microsomes and mitochondria of rat liver cells. The existence of these lindane metabolites was confirmed by Allsup and Walsh (1982) who demonstrated the presence of phenylmercapturic acid derivatives in rat urine by gas chromatography. Mercapturic acids are formed by the conjugation of glutathione with a xenobiotic, such as lindane, followed by the catabolic elimination of glutamic acid and glycine from the conjugate. The resulting cysteine moiety is subsequently acetylated to form the mercapturic acid. The formation of these acids represents an important mechanism in the detoxification of lindane (Allsup and Walsh, 1982).

Not only are lindane derivatives excreted in the form of phenylmercapturic acids but there is ample evidence that they are also excreted in the form of glucuronides and sulfate conjugates as well (Chadwick et al., 1978b). Urine from weanling female Sprague-Dawley rats fed diets containing 400 mg/kg (400 ppm) lindane was incubated for 24 hours with β-glucuronidase or sulfatase and then examined for glucuronide and sulfate conjugates of lindane metabolites. The glucuronide conjugates identified were 2,3,4,6-tetrachloro-2-cyclohexen-1-ol (12.8±2.30 μg), 2,4,5,6-tetrachloro-2-cyclohexen-1-ol (0.42±0.09 μg) and 2,3,4,5,6-pentachloro-2-cyclohexen-1-ol (23.5±4.50 μg). The sulfate conjugates identified were 2,3,4,6-tetrachloro-2-cyclohexen-1-ol (0.45±0.04 μg), 2,4,5,6-tetrachloro-2-cyclohexen-1-ol (0.04±0.002 μg), and 2,3,4,5,6-pentachloro-2-cyclohexen-1-ol (0.24±0.13 μg).

Apparently, in addition to its effects on accumulation of lindane derivatives as reported by Chadwick et al. (1978a), dietary fiber also affects excretion. Table III-3 shows the lindane metabolite content of feces and urine of female rats treated with lindane. The data represents two groups of animals: Group I was fed a low-fiber diet (LRD) and Group II was fed a

TABLE III-3

Effect of Fiber on Excretion of Lindane Metabolites[a]

	Diet[b]				
	Group 1 (LRD)	Group 2 (PLC)	Group 3 (LRD+P)	Group 4 (LRD+Ag)	Group 5 (LRD+Al)
Urine % of administered dose	7.85%	7.10%	9.70%	8.72%	8.45%
Feces % of administered dose	0.72%	4.12%	3.55%	1.04%	0.80%
Free chlorophenols in urine (dpm x 10^{-5})[c]	0.74	1.32	0.80	0.80	0.81
Conjugated chlorophenols in urine (dpm x 10^{-5})[c]	0.92	1.76	1.25	1.10	1.07

[a] Source: Chadwick et al., 1978a

[b] LRD = low residue diet; PLC = Purina lab chow; LRD+P = low residue diet plus 10% pectin; LRD+Ag = low residue diet plus 10% agar; LRD+Al = low residue diet plus 10% Alphacel.

[c] dpm (disintegrations per minute) after administration of labeled ^{14}C-lindane

high fiber diet (Purina laboratory chow). Only very small amounts of lindane derivates were excreted in the feces; urine was the major route of lindane excretion.

As can be seen from Table III-3, fiber facilitates the excretion of these chlorophenolic metabolites of lindane. Other types of fiber, such as those containing pectin, agar and Alphacel, gave results qualitatively similar to those reported for the laboratory chow.

Apparently administration of another insecticide can cause dramatic effects on the excretion of lindane. In a study in which the insecticide, kepone (0-1.5 mg/kg), was given orally to pregnant rats, followed by treatment with labeled lindane (1.66 mg/animal), also given orally, Chadwick et al. (1979) found that in the pups born of such treated females the kepone caused a much greater, dose-related, increase in the excretion of lindane itself and of lindane metabolites. The kepone pretreatment caused a greater relative excretion of the tetrachlorophenols compared with excretion of trichlorophenols.

Human Studies. Chromatographic analysis (Angerer et al., 1981) of urine from humans occupationally-exposed to HCH showed the presence of 10 chlorinated phenols (all isomers of di-, tri- and tetrachlorophenols and a pentachlorophenol).

The excretion of lindane in humans was studied by Zesch et al. (1982) who compared the excretion of the compound in scabies patients with that of healthy normal people. Healthy volunteers applied 0.3% lindane emulsion (30 g) over the entire suface of their bodies on 3 consecutive days.

Scabies patients took baths to which potassium permanganate had been added and then applied 50 g of a 0.3% lindane emulsion over their entire bodies. Serum lindane concentratons 2, 4, 6 and 8 hours after application were ~2, 4, 4.5 and 2.5 ng/mℓ in the healthy volunteers and ~45, 200, 85 and 60 ng/mℓ in the scabies patients. The highest serum concentrations of lindane were found 5.5 hours after application (5 ng/mℓ) in healthy volunteers and 4 hours after application (200 ng/mℓ) in scabies patients. The cumulative excretion of nonmetabolized lindane was almost the same in the healthy volunteers (70 μg) and the scabies patients (108 μg). Zesch et al. (1982) suggested that above a threshold amount in the serum, lindane cannot be completely eliminated but appears to undergo detoxication by tissue deposit. The value of this threshold concentration was not specified.

HCH is also eliminated in human milk. It is commonly detected in low concentrations. Herbst and Bodenstein (1972) reported that β-HCH accounts for 90% of the HCH found in milk, with α-HCH and γ-HCH accounting for the remaining 10%. As previously mentioned (see Human Studies section under Accumulation/Distribution), all five HCH isomers have been detected in human semen, suggesting another route of elimination in human males (Szymczynski and Waliszewski, 1981a).

Summary

Ingested lindane can be readily absorbed from the GI tract to the blood with an efficiency of 85% or more. In animal experiments, lindane and other HCH isomers accumulated in most of the organs of the body, accumulating preferentially in the fatty tissue and to a lesser degree in the brain. Very little of these compounds remained in the blood (the brain/blood ratio being as high as 20).

In humans, lindane, in the form of the antiscabies agent Kwell (a 1% lindane preparation), is readily absorbed through the skin to appear at appreciable levels thereafter in the blood, reaching a maximal blood level in 6 hours. Lindane was found among the agents in the blood of Love Canal area residents. In pregnant women, lindane and other HCH isomers (from exposure through environmental pollution arising from the use of t-HCH in insect control programs) are easily transferred to the fetus by way of the placental blood supply. There is also much accumulation of these compounds (particularly lindane) in mother's milk. Older mothers living in rural regions accumulate more HCH than do younger urban women. Greater (occupational) exposure to HCH has been correlated with greater levels of accumulation of these compounds in affected humans.

Lindane and other isomers of HCH are metabolized, after oral administration, to pentachlorocyclohexene, tetrachloro-derivatives of 1-hydroxycyclohexene, as well as isomers of mono-, di-, tri-, tetra- and pentachlorophenols, particularly under oxidizing conditions containing NADPH-generating systems. Mono-, di- and trichlorobenzenes have also been found as minor metabolites of HCH.

Many of these metabolites are excreted in the form of conjugates with glutathione (to form substituted arylmercapturic acids by an enzymatic process) as well as in the form of the original metabolites. Virtually all lindane and other HCH metabolites disappear from animal organs (including depot fat) within 14 days. No information on the whole-body half-life of lindane is available; Stein et al. (1980), however, reported a half-life for lindane in Wistar rat depot fat of 1-2 days. The vast majority of lindane metabolites and conjugation products (such as aryl-mercapturic acids, glucuronides and sulfates) are excreted by way of the urine with only very small amounts of HCH and metabolites being excreted by way of the feces and only a trace, if any, found as exhaled carbon dioxide.

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as lindane from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to lindane is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Detailed information concerning the occurrence of and exposure to lindane in the environment is presented in another document entitled Occurrence of Pesticides in Drinking Water, Food, and Air (Johnston et al., 1984). This chapter summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

In the Exposure Estimation section of this chapter, available information is presented on the range of human exposure and intake for lindane from drinking water, food and ambient air for the 70 kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources. However, the Summary section of this chapter provides some insight into the relative contributions of the three sources, especially drinking water, to the range of intake values suggested by the available data.

Exposure Estimation

Drinking Water. Levels of lindane in drinking water vary from one location to another. The highest level of lindane monitored in the available studies was 2 μg/ℓ in Oregon (Elliott, 1979), below the Maximum Contaminant Level (MCL) of 4 μg/ℓ. In the national studies, the highest level of lindane reported was 0.9 μg/ℓ (U.S. EPA, 1977). However, levels of lindane in drinking water typically appear to be somewhat lower than these levels. Analysis of the Rural Water Survey (RWS) (U.S. EPA, 1984) suggests that median levels of lindane in drinking water systems would be <0.002 μg/ℓ, since only 1 of 92 systems sampled contained a level of lindane >0.002 μg/ℓ. Lindane may not be present in drinking water in some areas. The available monitoring data are not sufficient to determine regional variations in exposure levels for lindane.

The daily intake of lindane from drinking water was estimated using the assumptions presented in Table IV-I and the values presented above. The estimates in Table IV-I indicate that the daily intake of lindane from drinking water ranges from 0.0-0.057 μg/kg/day. However, the values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Diet. Data are limited on the dietary intake of lindane in the United States. Daily food intake for adults and for infants and toddlers by food

TABLE IV-1

Estimated Intake of Lindane from Drinking Water*

Drinking Water Concentration (μg/ℓ)	Intake (μg/kg/day)
0.0	0.0
0.002	0.00006
0.9	0.026
2.0	0.057

*Assumptions: 70 kg man consuming 2 ℓ of water/day.

group was estimated by the FDA for fiscal year 1979 (FDA, 1982a,b) (Tables IV-II and IV-III). The estimates of daily food intake are based on analyses of composite food samples obtained in market basket surveys. Intake calculated on the basis of weight (μg/kg/day) is greatest for the toddler and lowest for the infant. For the adult male, the highest intakes of lindane result from consumption of the grain and cereal group; sugar and adjunct group; and meat, fish and poultry group. Grains and cereals are a significant source of intake of lindane for the infant, while vegetables and sugars and adjuncts are significant sources of intake for the toddler.

Additional data were obtained on the estimated total dietary intake of lindane for adults in the years 1974-1979 and for infants and toddlers in the years 1975-1979 (FDA, 1980a,b, 1982a,b) (Table IV-IV). The average total intakes for adults, infants and toddlers over the years studied was 0.0040, 0.0057 and 0.0125 μg/kg/day, respectively. For the years studied, there has been an identifiable trend toward decreased intake of lindane.

Using the above data, the daily intake of lindane is estimated to be 0.0038 μg/kg/day. This value does not account for variances in individual exposure.

It is expected that dietary levels of lindane vary somewhat with geographical location, with higher levels occurring in foods from areas near the sources of lindane exposure. However, because of insufficient data, no estimates could be made of variations in intake by geographical region.

TABLE IV-II

Estimated Daily Intake of Lindane by Food Class for Adult Male[a]

Food group[b]	Intake (μg/kg/day)[c]
II. Meat, fish and poultry	0.0009
III. Grains and cereals	0.0015
V. Leafy vegetables	0.00003
VII. Root vegetables	0.00002
VIII. Garden fruits	0.0001
XI. Sugars and adjuncts	0.0012
Total	0.0038

[a] Source: FDA, 1982a

[b] Includes only those groups that contained quantifiable levels of lindane.

[c] Obtained by dividing intake in μg/day by 69.1 kg for adult male.

TABLE IV-III

Estimated Daily Intake of Lindane by Food Class for 6-Month-Old Infant and 2-Year-Old Toddler[a]

Food group[b]	Intake (μg/kg/day)[c]	
	Infant	Toddler
III. Other dairy and substitutes	--	0.0003
IV. Meat, fish, and poultry	0.0002	0.0009
V. Grains and cereals	0.0012	--
VII. Vegetables	--	0.0013
X. Sugars and adjuncts	--	0.0036
Total	0.0014	0.0061

[a] Source: FDA, 1982b

[b] Includes only those groups that contained quantifiable levels of lindane.

[c] Values obtained by dividing intake in μg/day by 8.2 kg for infants and 13.7 kg for toddlers.

TABLE IV-IV

Estimated Total Daily Intake of Lindane for Adult Male, Infant, and Toddler*

Year	Intake (µg/kg/day)		
	Adult (male)	Infant (6 months)	Toddler (2 years)
1974	0.0084	--	--
1975	0.0031	0.0133	0.0341
1976	0.0026	0.0049	0.0096
1977	0.0038	0.0059	0.0081
1978	0.0024	0.0028	0.0046
1979	0.0038	0.0014	0.0061
Average	0.0040	0.0057	0.0125

*Source: FDA 1980a,b, 1982a,b

Tolerance levels established by the U.S. EPA for lindane in and on raw agricultural commodities are presented in Table IV-V.

Air. Levels of lindane in the atmosphere vary from one location to another. The highest level of lindane reported was 11.7 ng/m³ (0.0117 µg/m³) in Tennessee in 1970 (Kutz et al., 1976). Typical levels, however, are somewhat lower. An estimated mean level of lindane in ambient air, based on the information in Kutz et al. (1976), is 0.6 ng/m³ (0.0006 µg/m³). (However, this estimate is based on data from 1970-1972 and obtained in sampling locations with potentially high concentrations of pesticides in ambient air.) Additionally, concentrations of lindane are below the limits of detection in some areas and may be as low as 0.0 ng/m³. The available monitoring data are not sufficient to determine regional variations in levels of exposure to lindane.

The daily respiratory intake for lindane from air was estimated using the assumptions presented in Table IV-VI and the values presented above. The estimates in Table IV-VI indicate that daily lindane intake from air ranges from 0.0-0.0038 µg/kg/day. The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Summary

This section considers the relative contribution of drinking water, food, and ambient air to the total human exposure from these three sources. The data presented here indicate the potential total exposure to lindane that could occur if a population was exposed to specific combinations of lindane concentrations in drinking water, food, and ambient air.

TABLE IV-V

Tolerances for Lindane In and On Raw Agricultural Commodities

Commodity	Tolerance (µg/kg)
Apples	1000
Apricots	1000
Asparagus	1000
Avocados	1000
Broccoli	1000
Brussels sprouts	1000
Cabbage	1000
Cattle, fat of meat	7000
Cauliflower	1000
Celery	1000
Cherries	1000
Collards	1000
Cucumbers	3000
Eggplant	1000
Goats, fat of meat	7000
Grapes	1000
Guavas	1000
Hogs, fat of meat	4000
Horses, fat of meat	7000
Kale	1000
Kohlrabi	1000
Lettuce	3000
Mangoes	1000
Melons	3000
Mushrooms	3000
Mustard greens	1000
Nectarines	1000
Okra	1000

TABLE IV-V (cont.)

Commodity	Tolerance (μg/kg)
Onions, dry bulb	1000
Peaches	1000
Pears	1000
Pecans	10 N
Peppers	1000
Pineapples	1000
Plums (fresh prunes)	1000
Pumpkins	3000
Quinces	1000
Sheep, fat of meat	7000
Spinach	1000
Squash	3000
summer	3000
Strawberries	1000
Swiss chard	1000
Tomatoes	3000

*Source: 40 CFR 180.133, July 1, 1981

N = Negligible residues

TABLE IV-VI

Estimated Respiratory Intake of Lindane*

Air Concentration ($\mu g/m^3$)	Intake ($\mu g/kg/day$)
0.0	0.0
0.0006	0.0002
0.0117	0.0038

*Assumptions: 70 kg man inhaling 23 m^3 of air/day (ICRP, 1975).

Table IV-VII presents a general view of the total amount of lindane that may be received by an adult male from air, food and drinking water. Three separate exposure levels in air, four exposure levels in drinking water, and one exposure level in foods are shown in the table.

The data in Table IV-VII have been selected from an infinite number of possible combinations of concentrations for the three sources. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to lindane at any of the combined exposure levels. The data represent possible exposures based on the occurrence data and the estimated intake data.

A mean air level for lindane of 0.0006 μg/m³ was estimated. Assuming an air level of 0.0006 μg/m³ and the estimated lindane intake of 0.0040 μg/kg/day from foods, drinking water would be the predominant source of exposure to lindane at drinking water levels >0.15 μg/ℓ.

The total estimated intake of lindane is <0.1 μg/kg/day. This value is lower than the FAO/WHO acceptable daily intake of 10 μg/kg/day (FDA, 1982a) and a maximum safe level of 0.6 μg/kg/day calculated by the U.S. EPA (1976).

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for lindane by route of exposure. The relative dose received may vary from the relative intake. In addition, the relative effects of lindane on the body may vary by different routes of exposure.

TABLE IV-VII

Estimated Intake of Lindane from the Environment by Adult Males

Concentration in drinking water (μg/ℓ)	Estimated total intake in μg/kg/day (% from drinking water) based on a concentration in air (μg/m³) of:		
	Low (0.0)	Intermediate (0.0006)	High (0.0117)
Low (0.0)	0.0040 (0%)	0.0042 (0%)	0.0078 (0%)
Intermediate (0.002)	0.0041 (1.5%)	0.0043 (1.4%)	0.0079 (0.8%)
High (0.9)	0.030 (87%)	0.030 (87%)	0.034 (76%)
High (2.0)	0.061 (93%)	0.061 (93%)	0.065 (88%)

Intake from each source:

Drinking water:	0.0 μg/ℓ:	0.0 μg/kg/day
	0.002 μg/ℓ:	0.00006 μg/kg/day
	0.9 μg/ℓ:	0.026 μg/kg/day
	2.0 μg/ℓ:	0.057 μg/kg/day
Air:	0.0 μg/m³:	0.0 μg/kg/day
	0.0006 μg/m³:	0.0002 μg/kg/day
	0.0117 μg/m³:	0.0038 μg/kg/day
Food:	0.0040 μg/kg/day	

References

Elliott, W.M. 1979. Portland's public water supply -- pure and simple. Proc. Natl. Conf. Environ. Eng. ASCE, New York.

FDA (Food and Drug Administration). 1980a. Compliance program report of findings. FY 77 total diet studies -- Adult (7320.73). FDA, U.S. DHEW, Washington, DC.

FDA (Food and Drug Administration). 1980b. Compliance program report of findings. FY 77 total diet studies -- Infants and toddlers (7320.74). FDA, U.S. DHEW, Washington, DC.

FDA (Food and Drug Administration). 1982a. Compliance program report of findings. FY 79 total diet studies -- Adult (7305.002). FDA, U.S. DHEW, Washington, DC.

FDA (Food and Drug Administration). 1982b. Compliance program report of findings. FY 79 total diet studies -- Infants and toddlers (7305.002). FDA, U.S. DHEW, Washington, DC.

ICRP (International Commission on Radiological Protection). 1975. Report of the task group on reference man. ICRP Publ. 23, Pergamon Press, New York.

Johnston, P., F. Letkiewicz, D. Borum, et al. 1984. Occurrence of pesticides in drinking water, food, and air. Interim draft report. Prepared by JRB Associates, McLean, VA, for ODW, U.S. EPA, Washington, DC.

Kutz, F.W., A.R. Yobs and H.S.C. Yang. 1976. National pesticide monitoring programs. In: Air pollution from pesticides and agriculture processes, R.E. Lee, Ed. CRC Press, Cleveland, OH. p. 95-136.

U.S. EPA. 1976. National interim primary drinking water regulations. EPA-570/9-76-003. Office of Water Supply, U.S. EPA, Washington, DC.

U.S. EPA. 1977. Lindane: Position document 1. Special Pesticide Review Division, U.S. EPA, Washington, DC.

U.S. EPA. 1984. Rural water survey. Computer data provided by Department of Sociology, Cornell University, Ithaca, NY.

V. HEALTH EFFECTS ON ANIMALS

Acute Toxicity

Of the various HCH isomers, the greatest acute toxicity occurs with the γ-isomer. Toxicity varies with species of the organism and with route of administration [i.e., in order of most severe injury to least severe, i.v. > i.p. > subcutaneous (s.c.) > oral > dermal (Shirakowa, 1959)]. In general, HCH in oil and fat are associated with higher toxicity; the pure crystalline form is the least toxic form. Toxicity also varies with type of oil or solvent (Starek and Zabinski, 1970). Table V-1 summarizes the acute toxic effects observed in animals following exposure to lindane.

Two studies demonstrated greater sensitivity of young animals to lindane's toxic effects than adults of the same species (Shirakowa, 1959; Radaleff and Bushland, 1960). Fouts and Adamson (1959) suggested that this difference in sensitivity to lindane intoxication among young animals (before weaning) is due to low production of liver enzymes involved in the detoxification process in young animals. A similar sensitivity was observed among diseased and distressed animals (Chen, 1968).

The data on acute toxicity of lindane gathered up to 1977 were summarized in a review by Solomon et al. (1977a). Median lethal doses (LD_{50}) have been determined for various animals following administration of lindane by various routes (Table V-2).

In comparison with other chlorinated hydrocarbons, lindane has higher acute toxicity because it is rapidly absorbed. Visible clinical symptoms

TABLE V-1

Acute Toxic Effects of Lindane Exposure

Animal	Effects	Reference
Rats	neurobehavioral (increased activity and increased maze performance errors)	Farkas et al., 1976
Rabbits	neurotoxic (convulsions, spasms, coma)	Prasad, 1981
Lambs	neurobehavioral (blindness, aimless wandering, teeth grinding)	Harrison et al., 1980
Pigeons	behavioral (anorexia, depression), diarrhea, vomiting, death	Blakley, 1982

TABLE V-2

LD_{50} for Lindane in Animals

Route of Administration	Animal	LD_{50}* (mg/kg)
Oral	rat, guinea pig, rabbit, dog	60-230
	rat	125 (Farkas et al., 1976)
	rat (male)	88 (Gaines, 1969)
	rat (female)	91 (Gaines, 1969)
	rabbit	60 (Desi et al., 1978)
	mice	1000 (Wolfe and Esher, 1980)
	pigeon	400 (Blakley, 1982)
	human (adult)	840 (Engst et al., 1979)
	human (child)	180 (Engst et al., 1979)
Dermal	rat (male)	1000 (Gaines, 1969)
	rat (female)	91 (Gaines, 1969)
Subcutaneous	rat, guinea pig, rabbit	50-100
Intraperitoneal	rat	35-85
Intravenous	rabbit	6
Cutaneous	mouse, rabbit, rat, guinea pig	300-500
(dry application)	rabbit	4000
(in solvent)	rabbit	50

*All values obtained from von Oettingen (1955) unless otherwise noted.

are apparent soon after exposure (Lehman, 1951). The higher water solubility of lindane compared with other chlorinated hydrocarbons and its rapid absorption explain the narrow range between NOEL and lethal doses of γ-HCH relative to similar compounds, such as DDT (Gunther et al. 1968; Martin, 1971).

According to Solomon et al. (1977b) and Farkas et al. (1976), death is preceded by neurotoxic manifestations: tremor, hyperexcitability and finally convulsions. Farkas et al. (1976) reported an oral LD_{50} of lindane dissolved in oil for rats at 125 mg/kg. Desi et al. (1978) reported an oral LD_{50} for lindane administered in gelatin capsules in rabbits of 60 mg/kg.

In birds (Gallus domesticus) the oral LD_{50} of t-HCH (13% γ-HCH) administered in gelatin capsules is 596.8 mg/kg (Krishnakumari and Muralidhara, 1981). Thus, birds may be more resistant to the acute toxic effects than laboratory animals.

When pigeons were exposed to 2100 mg/kg (2100 ppm) lindane in their feed, the following symptoms were noted: diarrhea, vomiting, anorexia, depression and finally death (Blakley, 1982). An approximate LD_{50} of 400 mg/kg was noted in pigeons, however other studies have shown an LD_{50} of 2 g/kg in the Mallard duck. Other factors (poor body condition, lack of fat stores and cold stress) may have made the pigeons unusually sensitive to lindane.

Lambs were exposed to pasture land immediately following application of a superphosphate containing lindane (0.12%). Of 60 lambs, 15 exhibited blindness, aimless wandering and teeth grinding within 24 hours; symptoms regressed 24-48 hours after removal from the lindane-treated pasture. No deaths occurred and the affected lambs recovered fully. It was advised that lambs not be exposed to pastures treated with lindane for 14 days after treatment to allow some dissipation of the insecticide (Harrison et al., 1980).

Oral LD_{50} values for a metabolite of lindane, 2,3,4,5,6-pentachlorocyclohexene, were reported to equal 3690-4930 mg/kg in mice and 2930-4180 mg/kg in rats (Engst et al., 1979). Thus, it appears that animals are far more susceptible to the acute toxicity of the original HCH or lindane than to one of their metabolites. This might also suggest that the actual metabolite responsible for the acute toxicity of lindane and HCH is some substance other than the cyclohexene derivative.

In their study of the effects of lindane given at acute/toxic levels, Farkas et al. (1976) reported that the rats, when given subacute amounts of lindane (5-10 mg/kg), increased motor activity and maze performance errors. Prasad (1981) found that when rabbits were treated topically with 1% lindane, 11/21 showed convulsions, coma and spasms.

Subchronic and Chronic Toxicity

Chronic toxicity will be discussed in terms of general toxicity studies; toxicity of lindane and its isomers on the testis, adrenals and liver, and on the immune system; general biochemical changes induced by HCH isomers; toxicity in terms of embryologic and teratogenic effects; and toxicity in terms of mutagenicity and carcinogenicity.

General Toxicity. The Research and Consulting Company Ltd. (RCC, 1983) evaluated the effects of lindane on Wistar KFM-HAN (outbred) SPF rats, 20 of each sex/level. Lindane (99.85% pure) was added to the diet at levels of 0, 0.2, 0.8, 4, 20 and 100 ppm for a period of 12 weeks. Fifteen animals/group were sacrificed at the end of exposure while the remainder were sacrificed after an additional 6-week recovery period. The mean daily intake of lindane based upon measured food consumption equaled 0.02 and 0.06 mg/kg bw/day for the two lower doses. At 4, 20 and 100 ppm the intake for males averaged 0.29, 1.55 and 7.25 mg/kg bw, respectively, while females averaged 0.33, 1.67 and 7.90 mg/kg.

Lindane at all levels had no effect on mortality, food consumption, hematology or urinalysis. Decreased weight gains were detected only at the highest dose. Liver cytochrome P-450 levels were increased significantly in females at doses ≥0.8 ppm but only at 100 ppm in males. A dose-related increase in liver carboxylase was seen in female rats at all doses, but was not detected in males at any dose. Gross necropsy revealed the presence of diffuse gray foci in male rats at the 20 and 100 ppm levels. Histopathologic changes were confined to the liver and kidneys and occurred primarily at the 20 and 100 ppm levels. Hypertrophy was the only change seen in the liver. In the kidneys, tubular degeneration, hyaline droplets, tubular casts, tubular distension, interstitial nephritis and basophilic tubules were detected. The changes were more frequent and severe among males. From the information presented it appeared that the ability of the females to increase the amount of xenobiotic metabolizing enzymes in the liver may have reduced the toxic effects of lindane on the liver.

The primary effects at 4 ppm were liver hypertrophy and increased levels of cytochrome P-450. These are generally considered adaptive and not toxic manifestations. Other effects at this level were rare. On this basis it can be concluded that the NOAEL for this study is 4 ppm which is equivalent to a daily intake of 0.3 mg/kg.

Fitzhugh et al. (1950) fed groups of 10 male and 10 female Wistar rats (21 days old) γ-HCH in the crystalline form at 10, 100 and 800 ppm (~0.5, 5, 40 mg/kg bw) and in a 10% corn oil solution at 0, 5, 10, 50, 100, 400, 800 and 1600 ppm (~0, 0.25, 0.5, 2.5, 5, 20, 40 and 80 mg/kg bw). Most animals were allowed to live out their natural lives. At doses ≥100 ppm, liver cell hypertrophy and nephritic changes were observed. Lifespan was decreased by 20-40% by concentrations ≥400 ppm in oil carrier; lindane in the crystalline form did not result in decreased lifespan. The NOAEL was considered by the investigators to be 50 ppm in the diet.

Liver effects were also seen in another study designed to cover the lifespan of the test animals (Truhaut, 1954). Groups containing 10 male and 10 female rats received 25, 50 and 100 ppm lindane. There was no effect on the liver at 25 ppm, whereas at 50 ppm hypertrophy occurred and at 100 ppm signs of fatty degeneration were described.

Wolfe and Esher (1980) studied the general toxic and embryotoxic effects of exposure of the cotton mouse and the old-field mouse to lindane. For 8 months, lindane was added to the food at a dose level of 0.2 mg/g food (200 ppm). There were no differences between exposed and control animals in survival, growth or behavior of the neonates. The only significant effect of lindane was an increase in the number of litters produced in the lindane-treated mice.

Earl et al. (1970) fed lindane in the diet to dogs at levels of 7.5, 15.0 and 22.5 mg/kg bw/day for 24 weeks. Hematological findings included decreased numbers of reticulocytes and platelets, crenated red blood cells and a myeloid:erythroid ratio in excess of 750:1 at the highest dose level. Only slight histopathological effects were noted in the liver at doses $\geq$15 mg/kg. An increase in serum alkaline phosphatase level was found at all three doses. This study was difficult to evaluate since it was published only in abstract form.

In a study conducted by Fitzhugh et al. and reported by Lehman (1965), dogs (2/sex/group) were exposed to 0 or 15 ppm (~0.6 mg/kg bw) lindane in the diet for 63 weeks. No exposure effects were noted on mortality, body weight gains, organ weights, hematological values or histopathology.

Rivett et al. (1978) exposed beagle dogs to lindane for a period of 104 weeks. Four animals of each sex per group were fed lindane at levels of 25, 50 and 100 ppm in the diet for 104 weeks or 200 ppm for 32 weeks. Based on measured food consumption, actual lindane intake averaged 0.83, 1.60 and 2.92 mg/kg/day for the 25, 50 and 100 ppm groups, respectively. Virtually no neuropathological effects were noted (in terms of changes in electroencephalogram patterns) except some nonspecific neuronal irritation at the 200 ppm level. At 100 ppm, the liver was slightly enlarged and appeared darker than normal. A progressive elevation of alkaline phosphatase levels was noted at 100 and 200 ppm. The authors proposed a NOEL of 50 ppm (1.60 mg/kg/day).

Miniature swine are evidently resistant to the toxic effects of lindane. As reported in an abstract, Earl et al. (1970) fed swine up to 80 mg lindane/kg bw/day for 14 weeks. Hematological changes were not found but the liver showed only slight nonspecific changes.

Effects on Testis. Nigam et al. (1979) fed 65 mg/kg bw (500 ppm in the diet) t-HCH (containing all the HCH isomers including lindane) to 150 male mice (20-24 g in weight) for 10 months. They found increases in relative testicular weight (testis weight/total body weight) compared with controls. From the third month onward degenerative histopathology was observed in the seminiferous epithelium. Severe damage to spermatogonia was also seen. Dikshith et al. (1978b) found degenerative changes in the testes of guinea pigs following dermal administration of t-HCH at a dose of 100 mg/kg/day for 5-12 days.

Effects on the Immune System. Desi et al. (1978) studied the response of rabbits to *Salmonella typhi* vaccine following treatment with 1.5-12 mg lindane/kg bw given orally 5 times/week for 5-6 weeks and compared the immunologic behavior with normal, untreated animals. Six animals were used in each group. The treated rabbits displayed a dose-related decrease in immunologic titers, indicating immunosuppressive effects. Similar results were reported by Dewan et al. (1980) who found that male and female albino rats fed lindane (6.25 or 25 mg/kg in olive oil on alternate days for 35 days) displayed immunosuppressive behavior when challenged with *S. typhi* and *S. paratyphi* antigens. Again the effects were dose-dependent.

Roszkowski (1979) reported that oral doses of lindane (5 mg/kg/day for 90 days) had no effect on the following immunologic parameters in chickens: hemaglutinin and hemolysis titers, numbers of plaque-forming cells and splenic tissue reaction.

Neurologic and Behavioral Effects. Müller et al. (1981) studied the electroneurophysiological effects of HCH isomers on groups of 15 Wistar rats. The animals were fed diets containing each isomer for 30 days. Treatment with the α-isomer at doses of 5.1-106 mg/kg bw did not induce change in conduction velocity. Conduction delay was observed in animals receiving the β-isomer at both 66 and 271 mg/kg bw. A conduction delay found in the animals fed the γ-isomer was noted at a daily dose of 25 mg/kg but not at 12 or 1.3 mg/kg bw. The greatest delay was found in the case of the lindane metabolite γ-pentachlorocyclohexene (38-782 mg/kg bw).

Desi (1974) measured behavioral endpoints in Wistar rats (8 animals/group) exposed up to 40 days to lindane at daily intakes of 2.5, 5, 10 and 50 mg/kg bw. After ~2 weeks of exposure, maze running times and numbers of errors were significantly increased at dosages ≥5 mg/kg. The number of lever presses in an operant conditioning test (Skinner Box) was significantly increased even at the 2.5 mg/kg dose indicating an effect upon irritability.

Pygmy swine showed no clinical symptoms during or after 7 weeks exposure to 15, 30 or 45 mg/kg lindane. Food intake reduction and nervous system effects were seen at 75 mg/kg after 34 days and at 125 mg/kg after 22 days exposure (Earl et al., 1970).

While lindane is itself neurotoxic, it nevertheless seems to protect rats from the neurotoxicity of another toxicant, pentylenetetrazol (PTZ), which causes convulsions in rats. β-HCH is almost as potent as lindane in this regard, while α-HCH is far less potent as a protector against the neurotoxic effects of PTZ (Vohland et al., 1981). The effects of HCH isomers on convulsive or other neurotoxic effects of other agents, besides PTZ, has yet to be studied.

Additional studies on the protective effect of HCH on the convulsive effects of PTZ (Hulth et al., 1978) demonstrated that, after 3 days, lindane raised the PTZ convulsive threshold (i.e., decreased the ability of PTZ to cause convulsions) and increased the level of γ-aminobutyric acid (GABA) in the brain. During the first 2 days of lindane administration the convulsive threshold decreased, while the GABA content did not. α-HCH elevated both the convulsive threshold and GABA content.

Biochemical Effects in the Liver. Increases in liver weight accompanied by increases in cytochrome P-450 oxidase activity in the liver were noted by Parzefall et al. (1980) in rats treated with i.p. injections of α-HCH and with the metabolite β-pentachlorocyclohexene. The threshold values for observation of these effects (increased liver size and MFO activity) were 7.62-10.9 mg/kg/day (30-43 μmol/kg/day) in the case of the cyclohexene derivative and 0.291-0.495 mg/kg/day (1.0-1.7 μmol/kg/day) in the case of the α-HCH. However, on the basis of molar hepatic concentrations, β-pentachlorocyclohexane was 2-10 times more potent than α-HCH in inducing the observed hepatic effects.

In another study (Schulte-Hermann and Parzefall, 1981), female Wistar rats were treated orally with α-HCH in doses of 20 mg/kg/day, 200 mg/kg every second week, or 420 mg/kg every third week for up to 33 months. Following treatment, increases in liver size and DNA, RNA and protein content of the livers of up to 100% as well as increases up to 300% in drug-metabolizing enzymes in the liver were observed. After withdrawal from α-HCH treatment of 1-year duration, all liver values returned to normal. After a single dose of α-HCH, these effects persisted for up to 2 years post-treatment. Thereafter, normal amounts of DNA synthesis were found. Thus there were no protracted permanent effects of α-HCH treatment on the rat liver.

An additional study showing the effect of lindane and its metabolites on other enzyme systems was reported by Plass et al. (1981). Groups of male Wistar rats (5-8/group) were treated with either lindane, γ-pentachlorocyclohexene, pentachlorophenol, 2,3,4,5-tetrachlorophenol or 1,3,5-trichlorobenzene dissolved in sunflower oil and administered by gavage. Two series of experiments were performed. In the first series the substances were administered at doses of 2, 5, 10 and 20% of the corresponding LD_{50}s on 3 consecutive days; the animals were killed 24 hours after the last treatment. In the second series, rats were administered lindane or γ-pentachlorocyclohexene at a dose of 10% of the LD_{50} and were killed 12, 24, 48 and 72 hours after the single treatment. In the repeated administration studies, lindane and γ-pentachlorocyclohexene produced significant increases in the activities of N-demethylase and aniline hydroxylase at doses ≥5% of the LD_{50}. The level of cytochrome P-450 in the hepatic microsomes was also increased. The increases caused by lindane showed a clear dose-response relationship. In the single administration studies, lindane caused a significant increase in the activity of aminopyrine N-demethylase 24 hours after treatment. Demethylase activity was still increased 72 hours after lindane treatment. Aniline hydroxylase activity reached its peak level 48 hours after lindane and was nearly normal by 72 hours. The maximum level of cytochrome P-450 occurred at 24 hours with lindane.

Herbst et al. (1974) observed an increase in ascorbic acid in blood serum and urine, an increase in smooth endoplasmic reticulum in liver hepatocytes, and an increase in the glycogen content of individual cells related to increased glucuronic acid and ascorbic acid syntheses in rats given 5-20 mg/kg bw/day for short periods of time.

The effects of lindane on MFO and cytochrome P-450 levels in rat livers were investigated by Madhukar and Matsumura (1979). The treatment of Sprague-Dawley rats (male) with 25 mg/kg of lindane orally for 7 days resulted in the following in terms of percent of control activity: cytochrome P-450 activity, 61.8%; cytochrome b_5, 32.3%; and $NADPH_2$-cytochrome c reductase, 151.3%. Demethylation of benzphetamine and ethylmorphine was also stimulated. These results seem to differ from those of Lowy et al. (1977) who found that lindane, above a level of 20 ppm in the diet, caused increases in the level of cytochrome P-450. Lowy et al. (1977), however, did find increases of some other MFOs in agreement with the findings of Madhukar and Matsumura (1979). Thus, the evidence indicates that lindane increases MFO levels in the liver and either increases or decreases cytochrome P-450.

Liver enzymes other than drug-metabolizing enzymes and other critical biochemical factors are also affected by HCH (including lindane) treatment. Kraus et al. (1981) studied the effects of α- and γ-HCH and the metabolite pentachlorocyclohexene on glutathione-S-transferase activity in the livers of male Wistar rats. Treatment of the rats with 10 mg/kg lindane administered i.p. 5 times/day for 5 days resulted in a significant increase in the specific activity of glutathione-S-transferase for 3,4,5- and 3,4,6-pentachlorocyclohex-1-ene. Values in treated animals were 38% higher than in controls.

Other effects of lindane on liver enzymes have been found. γ-HCH (500 ppm, orally) inhibited the following enzymes in mouse liver: lactate dehydrogenase, malate dehydrogenase, isocitrate dehydrogenase and all enzymes of the sugar oxidative metabolic pathway (Thakore et al., 1981b). These decreased enzyme levels were reversed on discontinuation of the lindane feeding.

Karnik et al. (1981) studied the changes in liver enzymes during HCH-induced liver cancer development in mice. A pure inbred strain of Swiss mice was treated for 8 months with HCH (specific isomer not specified) at a dose level of 65 mg/kg bw (500 ppm in the diet). Again liver weights increased with HCH treatment, especially after neoplasia was observed. Activities of glucose-6-phosphatase and fructose-1,6-diphosphatase, decreased progressively with time of exposure. This was accompanied by a vast increase in glycogen accumulation in the liver during the first few months of feeding. When the feeding was halted before 6 months had elapsed, some reversibility of these biochemical effects was observed; the effects became irreversible after 8 months, well after the onset of hepatocellular cancer. An increase in liver cell endoplasmic reticulum and a depletion of glycogen storage in the developing tumor cells was also noted.

Dikshith et al. (1978b) studied the biochemical changes caused by t-HCH applied dermally to guinea pigs. Administration of 100 mg/kg/day resulted in no mortality while exposure to 200 mg/kg/day caused death to all animals within 5-12 days. Animals exposed to 100 mg/kg/day exhibited massive congestion and thickened blood vessels in the liver and degenerative changes in the testes. No changes were noted in the epididymis, brain, kidney, lungs or spleen. The biochemical changes observed include elevation of the levels of liver glutamic oxaloacetic transaminase and glutamic pyruvic transaminase. Serum levels of these enzymes also increased when the animals were treated dermally with HCH. While the serum alkaline phosphatase showed an increase, the increase in the liver enzyme was insignificant. Thus, effects of HCH on the blood system in the liver are accompanied by enzyme effects reflecting damage to the liver.

The enzyme levels of porphyrinogen carboxylase were studied in chick embryo livers following treatment with lindane (Taira and San Martin de Viale, 1980). The eggs of Leghorn and New Hampshire strain chickens were treated at doses of 0.5-3.0 mg lindane (in a DMSO vehicle) per egg; the eggs were incubated for 24 hours. The eggs were then broken and the livers were excised. In New Hampshire strain eggs, the liver porphyrin level doubled when treated with 1 mg/egg, while at 2 mg/egg, the porphyrin level almost tripled. In the New Hampshire strain at both dose levels, levels of the porphyrinogen carboxylase enzyme increased. In the Leghorn strain and in New Hampshire 1-day-old chicks, however, the level of the enzyme decreased.

A NOEL was determined for the effect of lindane on aminopyrine-N-demethylase, aniline hydroxylase and cytochrome P-450 concentration in rat liver microsomes (Lowy et al., 1977). Groups of eight male weanling Wistar rats were fed diets containing lindane at 0, 0.02, 0.05, 0.2, 2.0 and 12.0 mg/kg bw (based on 0, 0.2, 0.5, 2.0, 20.0 and 120 ppm in the diet and ingestion of 10% bw/day for immature animals) for 4 weeks. For each of these compounds, increases were observed at 20 mg/kg but not at 2.0 mg/kg bw. All these effects were dose-related with increasing levels of the biochemical parameters noted with increasing dosage of lindane. At the $p<0.95$ confidence interval, the NOEL of lindane was 0.016 mg/kg bw (0.16 ppm in the diet).

Biochemical Effects in the Brain, Adrenals and Kidneys. Enzyme levels in organs other than the liver have also been determined following treatment with lindane and other HCH isomers. Ca^{++}- and Mg^{++}-dependent ATPase activity was studied in rat brain cells *in vitro* at 10^{-5} M and 10^{-4} M concentrations of the various HCH isomers (Yamaguchi et al., 1979). The synaptic concentrations of the Ca^{++}-,Mg^{++}-ATPase were found to be lower as compared to controls by the following amounts (at the 10^{-5} M level): α-isomer, 13.2%; β-isomer, 12.6%; and γ-isomer, 33.1%. At the 10^{-4} M level these values were 32.2%, 16.8% and 42%, respectively. Thus, of the three isomers tested, the γ-isomer seems to be the most potent inhibitor of the brain synaptic Ca^{++}-,Mg^{++}-ATPase.

In another *in vitro* study, Riedel and Christensen (1979) showed that lindane treatment resulted in a decrease in ATPase (of unspecified origin) to 50% of control levels at a concentration of 3.75×10^{-4} M while, for comparison, mercuric chloride gave the same amount of inhibition at a concentration of 2.5×10^{-7} M. Thus, lindane has ~1/1000 the potency of mercuric chloride as an inhibitor of ATPase.

Shivanandappa et al. (1982) found definite hypertrophy of the adrenal glands on treatment of mice fed t-HCH over a period of 90 days. This was accompanied by an elevated accumulation of cholesterol and a sharp decrease in steroidogenic activity, along with histopathological effects at dose levels of 97.5 mg/kg bw (750 ppm) and above. No such effects were noted at doses of ~13 or 32.5 mg/kg bw (100 or 250 ppm in the diet). Based upon the above results a NOEL for t-HCH of 32.5 mg/kg bw could be proposed for adrenocortical effects in mice.

Tiwari et al. (1982b) reported a variety of biochemical alterations in both the liver and kidneys of rats given daily oral doses of 20 mg/kg bw lindane for 15 days. Decreased liver and increased serum levels of glutamic oxaloacetic transaminase were found [addition of ascorbic acid (vitamin C: 20 mg/100 g/day) restored this value to normality]. Brain inorganic pyrophosphatase and acetylcholinesterase activities were decreased on treatment with lindane, but these values were also at least partially restored when the diet was supplemented with ascorbic acid. Total liver lipid levels were increased on lindane treatment and further increased on supplementation with ascorbic acid. On the other hand ascorbic acid eliminated the increases in total liver phospholipids and neutral lipids. Ascorbic acid also restored to normality levels of liver monoglycerides and sterols (which decreased on treatment with lindane) and triglyceride and sterolesters (which increased on lindane treatment). Unfortunately only one dose level was used so a NOEL could not be determined.

An *in vitro* study of the effect of lindane on cultured C-6 glioma cells (Roux et al., 1980) showed that immediately upon treatment with lindane (ranging from 10^{-5} to 10^{-4} M), there was a sharp decrease in the uptake of α-aminoisobutyric acid (which is used to estimate the amount of amino acid uptake) and of uridine. In another study by these authors, wherein the cells were treated for 1 or 20 hours, uridine uptake again declined sharply; but an increase in α-aminoisobutyric acid uptake was observed indicating that lindane has a marked effect on the transport of amino acids and nucleosides into cells obtained from nervous tissue. This may well be related to the neurotoxic effects of lindane described above.

Teratogenic and Reproductive Effects. In a study in which female Wistar rats were dosed orally with lindane at levels ranging from 6.25-25 mg/kg bw from the 6th to 15th day of gestation, Khera et al. (1979) observed no statistically significant changes in numbers of dead or resorbed fetuses. Nor did they observe any type of birth defects in the offspring. These results were supported by the work of Palmer et al. (1978b), wherein rats were fed lindane at levels of 1.25, 2.5 and 5 mg/kg bw (25, 50 and 100 ppm in the diet) for three generations. No adverse effects of lindane on reproductive function and no malformations were observed. Similar negative results were found in a teratogenic study in pregnant rabbits fed lindane on gestation days 6-18 inclusive at levels equivalent to 5, 10 and 15 mg/kg bw and pregnant CFY rats fed the same doses of lindane on gestation days 6-16 inclusive (Palmer et al., 1978a), reinforcing the lack of teratogenicity of lindane in animals. Contrary to these studies, Dzierzawski (1977) reported a 2- to 20-fold increase in resorbed fetuses in hamsters treated with 20 and 40 mg/kg lindane on day 8 of pregnancy. Similar results were obtained in rats treated with 50 and 100 mg/kg on day 9 of pregnancy and 40 mg/kg doses on days 6, 8 and 10, and in rabbits treated with 40 and 60 mg/kg on day 9. While the majority of available information (i.e., three reports) seems to point to no net reproductive or teratogenic effects of lindane on mammals at lower doses, the report by Dzierzawski (1977) suggests that further studies may be necessary before a final conclusion is reached.

Studies in birds reveal somewhat different results. In a study of chicken and turkey embryos, Tullett et al. (1982) reported a loss of hatchability of embryos into live chicks following ingestion by the mother hens of tablets containing paraformaldehyde in combination with lindane (doses not specified). These authors cite earlier work (Sauter and Steele, 1972) showing that when fed to hens at a level of 0.1-10 ppm, lindane caused a distinct loss of hatchability of their eggs; however, another study (Whitehead et al., 1972) demonstrated no such effect at 100 ppm. Lindane caused malformations in Mallard chicks when the day 3 or day 8 eggs were immersed into aqueous emulsions containing high concentrations of lindane or sprayed with lindane dissolved in an oil vehicle (Hoffman and Eastin, 1982).

Mutagenic Effects. Shirasu et al. (1976) found that a mixture of α-, β- and γ-hexachlorocyclohexane (1 mg/mℓ) was negative in a rec-assay using H17 Rec^{+} and M45 Rec^{-} strains of *Bacillus subtilus* as well as in reversion assays on plates using autotrophic strains of *Escherichia coli* (WP2) and *Salmonella typhimurium* (TA1535, TA1536, TA1537 and TA1538). α-Hexachlorocyclohexane (10-20 μg/mℓ) was negative in reversion studies using a *Saccharomyces cervisiae* haploid strain XV185-14C (1×10^{8} cells/mℓ plated at 0.2 mℓ/plate) (Shahin and Von Barstel, 1977). Lawlor et al. (1979) tested lindane at five dose levels (levels not reported in the abstract) on four Salmonella strains (TA98, TA100, TA1535 and TA1537) both with and without metabolic activation by Aroclor 1254 induced rat liver microsomes with negative results. Hexachlorocyclohexane (dose levels and isomeric content not identified) was also negative using the four Ames tester strains of S. typhimurium (TA98, TA100, TA1535 and TA1538) (Purchase et al., 1978). Probst et al. (1981) tested lindane using eight histidine autotrophs of Salmonella (G46, TA1000, TA1535, TA1537, TA1538, TA98, C3076 and D3052) and two tryptophan autotrophs of E. coli (WP2 and WP2 uvr A^-) over a 10,000-fold concentration range. The results were negative for all strains.

Rohrborn (1977) also submitted positive evidence for the mutagenicity of lindane based on the host mediated assay of Gabridge and Legator (1969) as modified by Propping and Buselmaier (1971). The indicator strain used was S. typhimurium TA1535 which detected base pair substitutions. The host animals were male NMRI mice. Doses of 0.5, 5 and 50 mg lindane/kg were given orally. Increased bacterial killing and higher mutation frequencies were found at the highest dose (8.78-fold increase in mutation frequency at 50 mg/kg). Based on these results, lindane was considered a "weak mutagen" by the author.

Dominant lethal mutations were induced in male Swiss mice (6-8 weeks old) fed a diet containing 500 ppm technical grade HCH (~65 mg/kg bw) for 4, 6 and 8 months (Lakkad et al., 1982). Following the exposure periods the males were bred with females. Females were sacrificed at mid-gestation. A significant increase was noted in the number of dead implants and embryos in females bred with treated males as compared to controls. It is uncertain, however, whether lindane or one of the other isomers of hexachlorocyclohexane induced the mutations. In an earlier study, however, lindane administered to male mice by a single i.p. dose of 12.5, 25 or 50 mg/kg (corresponding to one-eighth, one-fourth or one-half of the LD_{50}) did not result in detectable increases in fetal deaths following mating with successive series of females during a 7-day period (U.S. EPA, 1973). Treatment of rats (SPF:THOM) by stomach tube at levels up to 15 mg/kg lindane also failed to induce dominant lethal effects (Rohrborn, 1977). Finally, no sex-linked recessive mutants were found in Drosophila melanogaster injected with an 0.001% solution of lindane (Benes and Sram, 1969).

Ishidate and Odashima (1977) reported that lindane (0.63-2.1 mg/mℓ) caused an increase in the frequencies of chromatid gaps and breaks in Chinese hamster fibroblasts in vitro. Tzoneva-Maneva et al. (1971) found that at concentrations of 5-10 ppm in the medium, lindane resulted in a significant inhibition of the division of cultured lymphocytes, but effects were not noted at 0.1, 0.5 or 1.0 ppm. A significant increase in the percentages of metaphases with structural damage to the chromosomes, however, was detected at concentrations as low as 0.5 ppm, with the damage increasing as the concentration increased. The authors compared the concentrations used with 0.5 ppm reported in the blood of people severely poisoned by lindane. Zimonjic et al. (1981) reported that lindane tested in human lymphocytes in vitro and in rat fibroblasts in vitro and in vivo caused decreases in the mitotic index and increases in structural aberrations. Unfortunately their report was in abstract form with no numerical values, dosages or methodology given.

Rohrborn (1977) carried out cytogenetic assays using Chinese hamsters treated with 0.125-12.5 mg/kg lindane by stomach tube. Metaphase plates were prepared from bone marrow cells. The author concluded that no significant increases in chromosome gaps, exchanges or other aberrations, compared with controls were found at any dose. At the highest dose tested, however, the frequency of gaps (15/600 metaphases) was significantly greater (p=0.0139) than the negative control (7/800 metaphases).

Lindane was ineffective in causing increases in micronuclei _in vitro_ using an epithelial cell line from the C3H mouse at doses up to 100 µg/mℓ (DeBrabander et al., 1976). _In vivo_ testing of lindane at a dose of 75 mg/kg bw in CBA male mice also failed to elicit an increase in micronuclei (Jenssen and Ramel, 1980). Similarly in human studies involving lindane producing workers, no appreciable increase in chromosome aberrations was noted (Kiraly et al., 1979).

Ahmed et al. (1977) reported that no increase in unscheduled DNA synthesis could be detected in SV-40 transformed human fibroblasts, either in the presence or absence of a rat liver microsomal activation system, at concentrations of 1 or 1000 µM lindane. No detectable increases in unscheduled DNA synthesis in human lymphocytes were detected following exposure to lindane (99.5% purity) in concentrations of 500 µg/mℓ (Rocchi et al., 1980). Probst et al. (1981) also reported that lindane failed to induce DNA repair in primary cultures of rat hepatocytes.

Lawlor et al. (1979), on the other hand, observed preferential killing of DNA repair deficient strains of bacteria although actual values were not listed in this abstract. Genotoxicity was measured by use of DNA repair spot tests and by liquid suspension tests utilizing E. coli strains WP2 uvr A^+recA^+ and WP100 uvrA^-rec A^- and Salmonella strains TA1978 uvrB^+ and TA1538uvrB^-. All DNA repair tests were conducted with and without metabolic activation.

Lindane has been shown to have chromosomal effects in a variety of plant species. Following treatment with lindane, polyploidy was noted in root tip cells of wheat and other grains (Zeller and Hauser, 1974), eight varieties of common pulses including Pesium sativurm (Baquar and Khan, 1971) and in Allium cepa roots (Nybom and Knutsson, 1947). In the latter two studies mitotic arrest was also noted. In addition, Sax and Sax (1968) reported that lindane crystals induced chromosome alterations in Allium cepa roots.

The evidence for the mutagenic activity of lindane is mixed. Only one study indicated a weak mutagenic effect of lindane at a dose of 50 mg/kg in mice. Another study indicated a positive dominant lethal mutation in male mice fed ~65 mg/kg bw lindane for 4-8 months. These cases, however, appear to be an exception as the majority of similar studies indicate negative results.

Carcinogenic Effects. There have been numerous studies of the carcinogenic effects of lindane in laboratory animals. Goto et al. (1972) fed groups of 10 male ICR-JCL mice (5 weeks old and weighing an average of 26.5 g) diets containing 300 and 600 ppm (~39 and 78 mg/kg bw) γ-HCH.

After 26 weeks of feeding, the mice were killed and their livers were then compared with those from control animals. The liver weights of the high-dose γ-HCH-treated mice averaged 4.1 g compared with a control value of 2.4 g. Liver neoplasms were detected in 5/10 (50%) mice given 600 ppm γ-HCH vs. 0/10 (0%) in the controls and in the low-dose group.

In a study by Nagasaki et al. (1972), groups of 20 male dd mice were fed the α-, β-, γ- and δ-isomers separately at levels of 100, 250 and 500 ppm in the diet (13, 32.5, 65 mg/kg bw) for 24 weeks. Multiple liver tumors as large as 2 cm in diameter were observed in all mice fed α-HCH at the 500 ppm level; however, γ-HCH did not produce liver tumors at any of the dosage levels tested. Didenko et al. (1973) found no tumors in mice fed γ-HCH by intragastic intubation at doses of 25 ppm (3.25 mg/kg bw) twice a week for 5 weeks.

Thorpe and Walker (1973) showed that CF1 mice were susceptible to the carcinogenic effects of γ-HCH. Thirty male and 30 female mice (4 weeks of age) were treated with 52 mg/kg bw (400 ppm) γ-HCH in the diet for a period of up to 110 weeks. Control groups consisted of 45 male and 45 female mice not given γ-HCH. By the 50th week, liver enlargement was detected in male and female mice given γ-HCH. The first liver neoplasm was observed after 12 months in a γ-HCH-treated female mouse. In the control groups the first liver neoplasm was found in a male at 18 months and a female at 23 months. At the end of the study 17% of the γ-HCH-treated males and 3% of the γ-HCH-treated females were still alive compared with 44% of the males and 32% of the females in the control groups. Based on finding the first neoplasms in any tissue in each group of mice, a highly significant increased incidence of hepatic neoplasms was observed in male and female mice ingesting γ-HCH. Liver neoplasms were found in 27/28 (96%) male mice and 20/21 (95%) female mice given γ-HCH ($p<0.001$), and in 11/45 (24%) male controls and 10/44 (23%) female controls. The incidence of neoplasms at sites other than the liver appeared to be decreased in the γ-HCH-treated animals. The γ-HCH-treated mice died early with neoplasms of the liver while the nontreated mice died early with extrahepatic neoplasms.

Induction of liver tumors in 6-week-old dd mice fed a basal diet containing 100, 300 or 600 ppm (13, 39 or 78 mg/kg bw) of γ-HCH for 32 weeks followed by 5-6 weeks of HCH-free diet was reported by Hanada et al. (1973). Liver tumors were found in 3/4 male mice and in 1/3 female mice receiving the 600 ppm dose. No tumors were found in controls or in mice fed 100 or 300 ppm γ-HCH. This study was of short duration compared with other carcinogenic studies using lindane. Also, the experimental groups (10-11 mice/group) were small.

Ito et al. (1973) treated groups of 20-40 male dd strain mice, 8 weeks old, with 0-65 mg/kg bw (0-500 ppm in the diet) of γ-HCH for 24 weeks. Tumors were not seen in control mice or in mice treated with γ-HCH.

In a study by Nagasaki et al. (1975), male dd mice (15-20 mice/group) ingested 50, 100, 250 or 500 ppm of γ-HCH for 24 weeks. At the higher doses, hyperplasia of centrolobular cells was seen in some animals, but neither hyperplastic nodules nor carcinomas of the liver were observed.

Herbst et al. (1975) found no increases in lymphatic leukemia, malignant hemangioendotheliomas or liver cell adenomas in Chbi:NMRI(SPF) strain mice fed γ-HCH at levels of 12.5, 25 and 50 ppm (1.625, 3.25, 6.5 mg/kg bw) in the diet for 80 weeks. There were 50 mice of each sex given each dose of lindane and 100 mice of each sex for controls. In another study (Weisse and Herbst, 1977), 500 NMRI (SPF) strain mice were fed lindane at the same concentrations as above (Herbst et al., 1975) for a period of 80 weeks. Compared with controls, there was no significant increase in tumors found in the liver. Furthermore, electron microscopy failed to provide evidence of γ-HCH-induced fine structural alterations in hepatic cells.

In a bioassay study (NCI, 1977) $B6C3F_1$ male and female mice, 35 days old, were fed lindane at two dose levels in the diet (80 and 160 mg/kg: 10.4 and 20.8 mg/kg bw) for 80 weeks. Groups of 50 mice of each sex were administered lindane at one of the two doses. Matched controls consisted of groups of 10 untreated mice of each sex. Pooled controls, consisting of the matched controls and 40 untreated male and 40 untreated female mice from other bioassays, were used for statistical evaluation. All surviving mice were sacrificed at 90-91 weeks. At least 88% of the males and 80% of the females survived to the end of the study. Survival rates were comparable for the treated and control groups within each sex and for the high-dose and low-dose groups. Necropsy and histopathologic examination revealed the random occurrence of a variety of neoplastic, proliferative, degenerative and inflammatory lesions in both treated and untreated mice, and a relatively high incidence of neoplastic lesions in the liver. Hepatocellular carcinomas were found in 2/10 (20%) matched control males, 5/49 (10%) pooled control males, 0/10 (0%) matched control females, 2/47 (4%) pooled control females, 9/46 (20%) high-dose males, 3/46 (7%) high-dose females, 19/49 (39%) low-dose males, and 2/47 (4%) low dose females. When compared with pooled controls, the incidence of hepatocellular carcinomas was significantly higher (according to the Fisher exact test) in the low-dose males (p=0.001).

Because of the high spontaneous incidence (20.8%) of hepatocellular carcinoma in $B6C3F_1$ male mice and because the incidence among high-dose males was not significantly increased, NCI (1977) concluded that the occurrence of these tumors in these mice could not be conclusively related to the administration of lindane under the conditions of this bioassay. On the other hand the incidence of hepatocellular carcinomas in low dose males, while not showing a significant increase compared with matched controls, did exhibit a highly statistically significant increase compared with pooled controls.

This conclusion was disputed by Reuber (1979). In a review of the raw data from the NCI (1977) study Reuber found liver carcinomas in 19/49 (39%) low-dose males, 12/46 (26%) high-dose males, and 5/49 (10%) control males. Reuber also reported an increased incidence of lymphosarcomas of the spleen in female mice ingesting lindane. Splenic neoplasms, incuding hyperplasia, were seen in 13/49 (27%) low-dose females and 27/48 (56%) high-dose females, compared with 1/10 (10%) in the female control group. Reuber concluded that lindane is carcinogenic for the liver of male mice and the spleen of female mice.

The results of studies of the carcinogenicity of lindane in mice are summarized in Table V-3.

Fitzhugh et al. (1950) fed groups of 10 male and female Wistar rats (21 days old) diets containing 5, 10, 50, 100, 400, 800 or 1600 ppm (0.25, 0.5, 2.5, 5, 20, 40, 80 mg/kg bw) γ-HCH incorporated in a 10% corn oil solution or dry γ-HCH at dosage levels of 10, 100 and 800 ppm (0.5, 5, 40 mg/kg bw). Most animals were allowed to live out their natural lives. No increase in tumor incidence was reported for any groups, however, not all organs were examined microscopically. Average lifespans were reduced at dosage levels of 800 ppm or more. Reuber (1979), in his review of the data from this study, determined that 5/74 female rats and 3/75 male rats treated with γ-HCH had liver neoplasms. In addition, lymphosarcomas of the lung were present in 7/74 females and 9/75 males receiving γ-HCH. In another study, Truhaut (1954) also reported no increase in tumor incidence in rats fed diets containing γ-HCH (25, 50 or 100 ppm: 1.25, 2.5 or 5 mg/kg bw) for 2 years.

Ito et al. (1975) fed 5-8 week old male Wistar rats (weighing 150-180 g) 500 ppm (25 mg/kg bw) for 24 or 48 weeks. At the end of 48 weeks, increased liver weights and slight hyperplasia of centrolobular cells were observed in treated rats.

In a bioassay of lindane (NCI, 1977), Osborne-Mendel rats in groups of 50 of each sex were administered lindane at time-weighted average doses of 236 or 472 ppm (11.8 or 23.6 mg/kg bw) for males and 135 or 270 ppm (6.75 or 13.5 mg/kg bw) for females. The lindane was administered in the diet for 80

TABLE V-3

Studies of Lindane Carcinogenicity in Mice

Dose*	Animal	Number of Survivors	Treatment Duration (weeks)	Post-Exposure Period (weeks)	Animals with Liver Tumors	Reference
0.0	10 M, ICR-JCL	NS	26		0	Goto et al., 1972
39	10 M, ICR-JCL	NS	26		0	
78	10 M, ICR-JCL	NS	26		5	
13	20 M, dd	NS	24		0	Nagasaki et al., 1972
32.5	20 M, dd	NS	24		0	
65	20 M, dd	NS	24		0	
0.0	30 M, CF1	5	up to 110		11	Thorpe and Walker, 1973
0.0	30 F, CF1	1	up to 110		10	
52	45 M, CF1	20	up to 110		20	
52	45 F, CF1	14	up to 110		27	
0.0	00-22 dd	14 M, 15 F		37-38	0	Hanada et al., 1973
13	20-22 dd	10 M, 8 F	32	5-6	0	
39	20-22 dd	9 M, 7 F	32	5-6	0	
78	20-22 dd	4 M, 3 F	32	5-6	3 M, 1 F	
0.0	20-40 M, dd	NS	24		0	Ito et al., 1973
13	20-40 M, dd	NS	24		0	
32.5	20-40 M, dd	NS	24		0	
65	20-40 M, dd	NS	24		0	
6.5	15-20 M, dd	NS	24		0	Nagasaki et al., 1975
13	15-20 M, dd	NS	24		0	
32.5	15-20 M, dd	NS	24		0	
65	15-20 M, dd	NS	24		0	

TABLE V-3 (cont.)

Dose*	Animal	Number of Survivors	Treatment Duration (weeks)	Post-Exposure Period (weeks)	Animals with Liver Tumors	Reference
0.0	100 M, 100 F, Chbi:NMRI (SPF)	NS	80		NS	Herbst et al., 1975
1.625	50 M, 50 F, Chbi:NMRI (SPF)	NS	80		NIC	
3.25	50 M, 50 F, Chbi:NMRI (SPF)	NS	80		NIC	
6.5	50 M, 50 F, Chbi:NMRI (SPF)	NS	80		NIC	
0.0	10 M, B6C3F1 (matched)	9		90	2	NCI, 1977
0.0	10 F, B6C3F1 (matched)	8		90	0	
0.0	50 M, B6C3F1 (pooled)	49		90	5	
0.0	50 F, B6C3F1 (pooled)	47		90	2	
10.4	50 M, B6C3F1	44	80	10	19	
10.4	50 F, B6C3F1	45	80	10	2	
20.8	50 M, B6C3F1	44	80	10	9	
20.8	50 F, B6C3F1	48	80	11	3	
0.0	50 M, B6C3F1	9		90	5	Reuber, 1979
0.0	10 F, B6C3F1	8		90	1 SN	
10.4	50 M, B6c3F1	44	80	10	19	
10.4	50 F, B6C3F1	45	80	10	13 SN	
20.8	50 M, B6C3F1	44	80	10	12	
20.8	50 F, B6C3F1	48	80	10	27 SN	

*mg/kg body weight

NS = Not specified; NIC = no increase over control levels; SN = splenic neoplasms weeks. Ten untreated rats of each sex served as matched controls. Pooled controls, consisting of the matched controls and 45 untreated males and 45 untreated females from other bioassays, were used for statistical analysis. Although a variety of neoplastic and proliferative lesions occurred in a random manner in both treated and control groups, most occurred with a low incidence and most were lesions commonly observed in Osborne-Mendel rats. Lesions that occasionally occurred only in treated animals were attributed to the small number of control animals rather than any harmful effect of lindane. The NCI study concluded that under the conditions of the bioassay, lindane was not carcinogenic in Osborne-Mendel rats.

Reuber (1979) reviewed the raw data and examined histological sections from the NCI (1977) bioassay. From this review, Reuber concluded that lindane is highly carcinogenic in Osborne-Mendel rats; induces benign and malignant neoplasms at all sites in male and female rats; and increases neoplasms of the endocrine organs, adrenal and pituitary glands, ovary and liver. Table V-4 compares the findings of the NCI (1977) report with those of the Reuber (1979) review.

Rivett et al. (1978) studied the effects of lindane on beagle dogs. Groups of four dogs of each sex (16-20 weeks of age) were administered 0, 25, 50 or 100 ppm (0, 1, 2, 4 mg/kg bw) lindane in the diet for 104 weeks or 200 ppm (8 mg/kg bw) for 32 weeks. Postmortem evaluation showed no adverse effects of lindane treatment were found in the groups receiving 0, 1 or 2 mg/kg bw. In the dogs given 4 mg/kg bw, the only unusual finding was a darkening of the liver. No abnormalities related to lindane were revealed by histologic examination. In dogs fed 8 mg/kg bw lindane, the livers were

TABLE V-4

Incidence of Primary Tumors in Osborne-Mendel Rats Fed Lindane in the Diet[a] Comparison of NCI Bioassay (1977) and Reuber (1979)

		Male[b]		Female[b]	
Organ	Dose	NCI	Reuber	NCI	Reuber
Liver	0 mg/kg				
	Matched	0/10	1/10	0/10	0/10
	Pooled	0/49	5/44	1/49	4/43
	Low	3/45	14/43	4/48	24/49
	High	2/45	16/40	2/45	16/47
Pituitary[c]	0 mg/kg				
	Matched	0/10	1/10	3/7	3/10
	Pooled	6/47	7/44	6/46	9/43
	Low	3/32	16/43	14/45	29/49
	High	1/35	16/40	8/41	30/47
Thyroid	0 mg/kg				
	Matched	1/6	4/10	0/8	1/10
	Pooled	3/42	8/44	0/48	3/43
	Low	6/37	18/43	2/44	12/49
	High	4/37	11/40	1/42	13/47
Adrenal[c]	0 mg/kg				
	Matched	1/10	4/10	0/9	1/10
	Pooled	2/54	7/44	0/51	3/43
	Low	0/37	15/43	3/42	28/49
	High	1/38	24/40	2/44	20/47
Ovary	0 mg/kg				
	Matched	NA	NA	0/8	0/10
	Pooled	NA	NA	NR	0/43
	Low	NA	NA	0/46	22/49
	High	NA	NA	1/44	27/47

[a] Treated males received time-weighted average doses of 236 or 472 mg/kg in feed and females received 135 or 270 mg/kg in feed.

[b] Number of tumor-bearing animals/number of animals examined at site.

[c] NCI study included only adenomas while the Reuber review considered adenomas and carcinomas.

NA = Not applicable; NR = Not reported

found to be dark, friable and slightly enlarged (4.22% mean body weight compared with 3.06% for controls). The cut surfaces had a granular appearance. No significant histopathological findings were found in the liver or any other organ or tissue examined. Because of the short duration of this study, an assessment of the carcinogenicity of lindane in dogs is not possible.

Summary

HCH isomers exhibit toxicity to a large number of systems in laboratory animals with a greater degree of acute toxicity observed in mammals than in birds. The major systems affected by HCH isomers (including lindane) are the liver, adrenals, immune system, nervous system and the testis. In the liver the effect is usually an increase in size. This is especially true when the animals are treated either with t-HCH (containing all HCH isomers) or with α-HCH. Necrosis of the testis is noted with much cellular degradation on treatment with t-HCH. Lindane treatment causes immunosuppression. Neurophysiological function decreases and behavioral effects are noted after treatment with β-HCH, with lesser effects for the γ-isomer (lindane); the α-isomer was not found to be neurotoxic. Lindane also causes hypertrophy of the adrenal gland. Some enzyme levels in the liver are enhanced by treatment with α- or γ-HCH and their pentachlorocyclohexene metabolite. These enzymes include glutathione-S-transferase and some of the MFOs (all drug-metabolizing enzymes). Other liver enzymes (serum glutamic oxaloacetic transaminase, alkaline phosphatase) are inhibited. ATPase enzymes in the brain are inhibited by treatment with HCH isomers. Some of the effects of HCH isomers on enzyme levels and other biochemical factors can be eliminated, at least partially, by treatment coincidently with ascorbic acid.

Uptake of amino acids and uridine into cultured brain-derived cells are inhibited by lindane.

There was no consensus showing consistent reproductive or teratogenic effects caused by HCH isomers, including lindane, in the few studies reported in the literature. There was, however, one report of dominant-lethal sperm mutation enhancement by treatment of male animals with t-HCH. Most reports show HCH to be nonteratogenic.

To date, the preponderance of evidence indicates that lindane is carcinogenic in some strains of mice. The susceptible strains are CF1 (Thorpe and Walker, 1973), ICR-JCL (Goto et al., 1972), $B6C3F_1$ (NCI, 1977) and dd mice (Hanada et al., 1973).

The mechanism of these toxic effects will be assessed in greater detail in Chapter VII of this document. However, the biochemical changes described in both liver and brain are consistent with the gross lesions observed in both organs following HCH treatment.

VI. HEALTH EFFECTS IN HUMANS

Acute Toxicity

Reports have been made of lindane causing death or serious toxic effects in humans when taken in large doses, particularly by oral ingestion.

Powell (1980) reported that a 14-month-old infant with scabies accidentally swallowed 5 mℓ of a solution of 1% HCH. Within minutes the child became agitated and irritable, had abnormal limb jerking, and after 15 minutes suffered a 7-minute severe, generalized convulsion. No neurological signs were found at the time of complete medical examination and the child was completely asymptomatic 12 hours later.

An earlier account covering the effects of lindane on a much larger sample of humans was reported by Nantel et al. (1977). These authors reported a group of 50 persons who accidentally ingested food contaminated with lindane (as found by gas chromatography study of the food and of gastric contents from one of the exposed humans). Within hours, most subjects complained of nausea, vomiting, diarrhea, headaches, dizziness and paresthesia. Twenty patients experienced grand mal seizures and one patient, a 35-year-old male, suffered from epilepsy, metabolic acidosis and later developed renal insufficiency as well as myolysis and myoglobinuria in addition to hypertensive crisis, pancreatitis and superficial vein thrombophlebitis.

Pernov and Kyurkchiyev (1974) reported the case of a 42-year-old man who developed depression, headache, emesis, asthenia, epileptiform attacks, sleeplessness, profuse perspiration, pathologically increased tendon reflex, finger tremor, oral automatism, bilateral Marinesiu-Radovici reflex, Romberg's sign, and Hoffmann's and Troemmer's signs in the upper extremities following acute γ-HCH poisoning. Concentrations of γ-HCH measured several weeks after the poisoning were 0.1-0.5 mg/ℓ in the blood and 0.2 mg/ℓ in the cerebrospinal fluid. Treatment with barbiturates, sedatives, glucose, and vitamins C and B_{12} was successful.

Davies et al. (1983) reported two cases of lindane poisoning. A 2-month-old infant died after having been treated with lindane lotion (1%) over his whole body for an 18-hour period. The lindane was washed off 24 hours before death. Autopsy revealed a level of 110 μg/kg (110 ppb) in the child's brain and 33.3 μg/ℓ (33.3 ppb) in the blood. In the other case, a 16-year-old mentally-retarded boy ingested 392 g of 1% lindane shampoo. Immediate effects included deep coma and low blood pressure (96/62 mm Hg). Abnormal eye responses, especially low reactivity to light and the lack of corneal reflexes, and some quadriplegia were evident. A second gastric lavage revealed 2565 μg of lindane. The initial serum lindane concentration was 206 mg/ℓ (206 ppm) and decreased to 1.0 μg/ℓ (1.0 ppb) after 25 days. Treatment included phenytoin sodium, diazepam and curare for seizures, forced diuresis, and cholestyramine resin. The patient recovered 12 days after the lindane ingestion.

Munk and Nantel (1977) reported the case of a 35-year-old man who ingested food containing ~15-30 mℓ of lindane. Grand mal epileptic seizures and severe acidemia developed within 30 minutes and recurred for ~2 hours. One day after admission the serum concentration of lindane was 600 μg/ℓ.

Muscle weakness and pain, headaches, episodic hypertension, myoglobulinuria, acute renal failure, and anemia were also noted. Pancreatitis developed 13 days after ingestion. A symmetric, predominantly proximal myopathy developed and a muscle biopsy on day 15 demonstrated widespread necrosis and regeneration of muscle fibers. During the year that followed, the patient complained of poor memory, weakness, and loss of libido. After 1 year, all symptoms disappeared.

Wheeler (1977) reported the case of a 1-year-old boy who accidently received ~5 mℓ (1 teaspoon) of 1% lindane orally after application of 100 ng topically (total dose 15 ng/kg). Low blood pressure (90/60), seizures, and difficulty in controlling eye movements were reported. No changes in blood chemistry were noted and no quantitative measure of lindane in the blood was determined. Diazepam treatment resulted in termination of the seizures. The boy recovered after 6 hours and returned to normal.

Matsuoka (1981) reported the case of a 7-year-old boy with tuberous sclerosis who experienced convulsions after the application of topical γ-HCH. The child had had no convulsions for the 6 months before the two petit mal seizures that occurred within 12 hours of lindane application. The use of γ-HCH is not recommended for patients with scabies and a decreased threshold for convulsions.

Telch and Jarvis (1982) reported a case of excessive dermal exposure to lindane. An 18-month-old boy treated dermally with a lindane lotion that was allowed to stay on the body for more than 12 hours developed seizures and became disoriented and lethargic. The initial serum level of lindane was 0.45 mg/ℓ (0.45 ppm) that declined to 0.029 mg/ℓ (0.029 ppm) after 96 hours. The boy recovered within 2 days. The authors recommended that no patient be exposed to lindane dermally for more than 6 hours. Bargman (1982) contested this advice, saying that even within 6 hours, the lindane can be absorbed to a degree capable of yielding toxic results.

Pramanik and Hansen (1979) reported that treatment of a premature, malnourished infant with one application of 1% lindane resulted in a serum level of 100 μg/ℓ; this was 17 times greater than expected (6.0 μg/ℓ) for a single topical application. The patient developed seizures and other abnormal neurological signs. In another child (2-year-old boy), repeated applications of small amounts of 1% lindane to areas of dermatitis and excoriations on the skin over a 2-week period resulted in a level of 0.012 μg/mℓ in the blood 16 hours after the last application. Based on these experiences, the authors cautioned against the use of lindane as a medication in children less than 1 year old, and in badly excoriated or pregnant patients. This advice was sharply challenged in a communication by Rasmussen (1980) who pointed out that toxicity rarely occurs in children receiving lindane as prescribed.

Kramer et al. (1980) used an algorithm to investigate the quality of evidence in reported cases of adverse drug reaction (ADR) to 1% γ-HCH (Kwell). Of 53 reported cases of alleged γ-HCH toxicity, 37 were associated with lindane insecticide. Evaluation of these 37 cases revealed 34 cases rated as probable or definite adverse reactions to lindane. Of 23 cases rated probable, acute effects included neurological manifestations in 4 patients (2 seizures alone, 1 CNS stimulation, 1 peripheral neuropathy), and vomiting in 4 patients. The major acute toxic manifestations in the 11 cases rated definite for ADR to lindane were seizures alone (1 case) and seizures and coma (2 cases). Of the 26 reported cases of toxicity to Kwell (1% γ-HCH), only 6 were rated as high as probable. The major acute toxic manifestation in these cases was seizures and all occurred in children 10 years old or younger. In this review Kramer et al. (1980) concluded that 1% γ-HCH (Kwell) is an extraordinarily safe medication when used according to instructions. The drug, however, may cause seizures, especially in young children, when given in excessive dosage or accidentally ingested.

Lindane has also been identified as a probable causative agent in a case of Henoch-Schonlein (anaphylactoid) purpura (Fagan, 1981) that developed in a 9-year-old boy treated with 1% Kwell shampoo. A skin rash on both lower legs and on the buttocks appeared 6 days after treatment and became purpuric within 2 days. Abdominal pain and severe vomiting were noted. Because of the closeness in time of the treatment and the appearance of these symptoms, Fagan contended (but could not prove) that the child experienced a hypersensitivity reaction to lindane in the Kwell preparation.

While numerous toxic effects associated with lindane have been described, Purres (1982) reported that no serious side effects were seen in a 20-year-old man who used Kwellada (γ-HCH solution in Canada) on a regular basis at a rate of ~120 mℓ (4 ounces/week) for 1.5 years. Skin irritation was present, but laboratory tests were normal. Since 1960, Kwellada has been available without a prescription in Canada. No significant ill effects have been reported despite the opportunity for inappropriate use.

These reports indicate that the acute effects of lindane resulting from either excessive dermal or oral intake include functional alterations in the nervous system in the form of seizures and uncontrollable eye movements, and organ pathology related to renal failure and muscle degeneration. All these effects appear to be reversible, with full recovery within 1 year of exposure. However, if the intake exceeds ~100 mg/kg of body weight, the effect could be death, especially in infants.

Chronic Effects

Kazahevich (1974) reported a variety of symptoms (headache, vertigo and irritation to the skin, eyes and respiratory tract mucosa) in workers occupationally exposed to t-HCH. Some workers exhibited apparent disturbances of carbohydrate and lipid metabolism and dysfunction of the hypothalamo-pituitary-adrenal system. Similar findings were reported by Besuglyi et al. (1973) in 88 exposed persons with headache, vertigo and irritation of the skin, eyes and respiratory tract mucosa being the most common complaints.

Sasinovich et al. (1974) studied 59 females and 29 males exposed occupationally to HCH for periods ranging from 11-23 years. Biochemical manifestations of toxic hepatitis included pathological changes in the hepatobiliary system (55% of the workers) with 33% having chronic hepatitis and 5% chronic pancreatitis. Sixty percent of all the subjects exhibited some form of biochemical abnormality.

As discussed under Acute Toxicity, Kramer et al. (1980) used an algorithm to investigate the quality of evidence in reported cases of toxicity to lindane. Of the 37 cases associated with lindane insecticide, chronic effects were rated as probable in 11 cases of aplastic anemia and 3 cases of red cell hypoplasia. The major chronic toxic manifestation in the cases rated definite for adverse drug reaction to lindane was aplastic anemia (2 cases). Of the 26 reported cases of toxicity to Kwell (1% γ-HCH) none exhibited chronic effects.

The effects of lindane on the levels of sex hormones were studied in 54 men (average age 40 years) who were occupationally-exposed to lindane for an average of 8 years (Tomczak et al., 1981). When compared with a matched group of 20 unexposed controls, the exposed group was found to have increased levels of luteinizing hormone (geometric mean of 8.8 mIU/mℓ compared with 5.7 mIU/mℓ in controls). There were no significant differences in the levels of follicle stimulating hormone or testosterone between the exposed and unexposed groups. These results indicate that HCH exposure may lead to a disturbance of sex hormone regulation. Further investigations will be necessary to determine the pathological significance of these alterations.

The frequency of chromosomal aberrations was studied in factory workers producing insecticides (Kiraly et al., 1979). Lymphocytes, extracted from peripheral blood samples obtained from exposed workers and controls, were cultured for 48 hours and then examined for chromatid-type and labile and stable chromosome-type aberrations. At least 50 metaphases were evaluated for each individual included in the study. When compared with a control group comprising 14 factory employees (engineers, technicians and office staff) never directly exposed to pesticides, lindane-producing workers (exposure dose and duration not given) showed no appreciable increase in the frequency of chromosome aberrations.

Baumann et al. (1980) studied 60 male workers (mean age, 42±10 years) at a chemical factory employed in the production of lindane for 1-30 years (mean duration 10±9 years). Twenty clerks having no occupational exposure to hazardous substances served as a control group. In contrast to the control persons, none of whom had HCH concentrations in serum above the respective detection limits, the values determined in serum of the exposed workers were in the following ranges: α-HCH, 10-273 μg/ℓ; β-HCH, 17-760 μg/ℓ; and γ-HCH, 5-188 μg/ℓ. Adipose tissue concentrations in the exposed workers were in the following ranges: α-HCH, 1-15 mg/kg; β-HCH, 18-103 mg/kg; and γ-HCH, 0-11 mg/kg extractable lipids.

In a follow-up study utilizing most of the same subjects (Baumann et al., 1981), a group of 60 workers (average age 40.4 years) occupationally-exposed for an average of 7.2 years were compared with two control groups of 20 clerks and 20 dairy workers of the same age distribution having no contact with hazardous substances. Forefinger tremor, manual skill tested by means of a tracking task, and nerve conduction velocity were not detectably altered in the occupationally-exposed group. The authors concluded that even after years or decades of occupational HCH exposure in this study, no signs of neuromuscular impairment could be ascertained.

Brassow et al. (1981) analyzed blood samples from the same group of subjects reported on in the Baumann et al. (1981) study. No significant differences between exposed workers and controls were noted in liver function enzymes (glutamate oxaloacetic transaminase, glutamate pyruvate transaminase, lactate dehydrogenase), hemoglobin content, total red and white cell counts, platelet counts, cholinesterase, triglycerides, cholesterol and urea. Exposed workers exhibited significantly lower lymphocyte counts (but higher polymorphonuclear leukocyte counts), lower blood concentrations of creatinine, and lower uric acid levels in the serum. These differences however, did not seem to be associated with any clinical abnormalities in the exposed workers. Cancer was not reported as an endpoint in these studies. Physical examination, however, did not reveal any specific pathological signs, especially hepatomegalia.

Blood Dyscrasias. A single case of hypochromic anemia was attributed to lindane exposure (Morgan et al., 1980). A 2.5-year-old boy had been exposed to excessive amounts of HCH by way of an HCH vaporizer that had been in constant use in the patient's home for a period of 7 years before the child's admission to the hospital. Two months before admission, the child suffered grand mal seizures. He was found to have low blood pressure (80/42). These symptoms were characteristic of acute toxic exposure to lindane. Other symptoms noted were excessively low levels of hemoglobin (4.3 g/dl), hematocrit (12%) and white blood cell count (4300 cells/mm^3). His serum iron was elevated to 245 μg/dl (normal 87-150); the child had been taking iron supplements for 2 weeks before admission. The patient's blood picture returned to normal by 19 weeks post-admission following removal from HCH exposure and treatment with phenobarbital, vitamins and iron. However, a definite causal relationship between HCH and the anemia was not established. Difficulties in establishing such a linkage in this case are due to the failure to observe any anemia during a very long period (2.5 years) after the start of lindane exposure and the continuation of improvement while HCH remained detectable in the patient's blood. The authors criticized previous reports of lindane causation of anemia and challenged the concept that lindane caused hypochromic anemia in man.

Possible mortality resulting from lindane treatment was alleged by Crissman (1980) who reported that his brother died of aplastic anemia following mishandling of the pesticide. The author believes this effect may have been due to genetic predisposition or unusual hypersensitivity.

Thus, there is at best only a conjectural linkage of lindane with anemia in man. While lindane may cause anemia, the patient data are inconclusive.

Although lindane has only an equivocal effect on red blood cells, it appears to have a very definite inhibitory effect on white blood cells (lymphocytes) *in vitro*. In a study conducted by Roux et al. (1979), 10^{-4} M lindane sharply inhibited protein, DNA and RNA synthesis in cultured lymphocytes, either in the unstimulated, phytohemagglutinin (PHA)-stimulated, or in the lymphoblast state. Lindane treatment resulted in sharply inhibited PHA-induced mitogenesis in the exposed lymphocytes.

Birth and Reproductive Effects. Wassermann et al. (1982) studied the effects of organochlorine compounds on premature delivery in humans. Higher levels of lindane were found in the serum of 17 women having had premature delivery (15 ppb) than in control women (4.3 ppb). These values were determined at the time of the premature delivery. This was also true of women with high DDT levels.

Saxena et al. (1980) reported that the incidence of abortions as well as premature labor increased with blood concentration of lindane. Mean blood level of lindane in 20 women who underwent full term labor was 18.50 ppb compared with 56.09 ppb in 20 women who experienced premature labor and abortions. Mean lindane level in placental tissue of full-term births was 8.56 ppb compared with 25.44 ppb in placental tissue from premature labor and abortions. Blood and placental levels of other chlorinated hydrocarbon pesticides were also higher in the premature pesticide group. Saxena et al. (1981) hypothesized that organochlorine insecticides, including lindane, may act as antagonists to pregnancy.

Rasmussen (1981) reviewed the toxicity of dermally-applied 1% concentrations of lindane in humans and concluded that lindane should continue to be used as a therapeutic agent for children of all ages since no conclusive evidence linking human exposure to lindane with anemias or other blood dyscrasias, mutagenesis, teratogenesis or carcinogenesis have been established. In the absence of any data to the contrary, lindane appears to be a perfectly safe agent in humans if properly used with very moderate dermal exposure. Rasmussen based his conclusions on the following considerations: 1) Kwell has been given over the last 10 years (before 1981) to 23 million patients with so few adverse effects reported that such rare occurrences usually merit special case reports; 2) carcinogenicity has been reported only in rodent livers at high doses and not in humans; and 3) no significant teratogenic or blood dyscrasia causing effects have been definitively linked to exposure to lindane.

Summary

Lindane ingestion or excessive dermal application resulted in CNS effects reflected in the form of epileptic-like seizures. Only equivocal effects of lindane on the blood cells, including possible anemia, have been reported. More consistent effects of lindane on the lymphocytes of humans have been reported with evidence of lower total lymphocyte counts and lower responses to lymphocyte mitogens being induced. There have also been several reports indicating lindane as a cause of increased spontaneous abortion in exposed women and as a possible cause of nervous system disorder in human neonates. However, since these reports are so few in number and arise from only a few groups of investigators, it is premature to describe lindane as an agent causing reproductive and neonatal abnormalities.

No evidence was reported to establish that lindane is a human carcinogen. In the Baumann et al. (1981) and Brassow et al. (1981) studies, only apparently well workers were evaluated. Any individuals that were either no longer employed or deceased as a result of cancer would not be included in these studies. Long-term follow-up of cases of exposure and accidental ingestion are needed to determine if lindane is a human carcinogen. To date, no such study has been reported. Thus, conclusive evidence does not exist to indicate that lindane is or is not a carcinogenic agent in humans.

VII. MECHANISMS OF TOXICITY

The toxicity of lindane and other HCH isomers was reviewed in Chapters V and VI. In animal models, lindane and the α and β isomers of HCH caused neurotoxicity, damage to the liver, damage to the immune system and cancer. In humans, there is definite evidence of neurotoxicity, especially at high doses. There is also some possibility of blood dyscrasias, although the evidence is highly contradictory. Effects on the immune system in humans have been reported as well as birth and reproductive effects. In this chapter, the possible biological mechanisms that give rise to such toxic effects will be presented.

Lindane, at high concentrations, has been shown to be a cytotoxic agent to cells in culture. Desi et al. (1977) showed that 250 mg/ℓ growth medium (250 ppm) lindane caused cytotoxicity to a monkey kidney cell line while at 100 mg/ℓ growth medium (100 ppm) only mild damage was noted. The cytotoxicity was attributed to damage to the cell membrane resulting in a decrease in the ability of the cells to maintain the cell-cell contact required for cell viability.

Neurotoxicity Studies

In a study of the effects of various chlorinated hydrocarbon insecticides on laboratory-constructed lipid bilayers, Omann and Lakowicz (1982) demonstrated that HCH isomers interact with synthetic membranes. Interaction was demonstrated by the quenching of the fluorescence of alkyl-derivatives of carbazole that was covalently bound to phospholipids comprising the synthetic membrane. Extensive quenching was noted, indicating interaction with the synthetic membrane. Of the three common HCH isomers, lindane was the most potent reactor with the membranes followed by the α- and then the β-isomer, following the order of solubility of these isomers in various organic solvents. This suggests that the interaction with the synthetic membranes may well be in the form of dissolution of the compound within the membrane lipids, rather than some specific interaction with membrane receptors. In any case, the neurotoxic effects of lindane and other HCH isomers may be related to interaction with neural cell membranes. This was also supported by the close similarity of interactions of HCH with synthetic membranes as compared with the effects of anesthetics known to interact with neural cell membranes.

Another study that demonstrated reaction of lindane with membranes was conducted by Antunes-Madeira and Madeira (1979). Lindane (10^{-5} to 10^{-4} M) was a mildly potent agent in increasing the permeability of a model liposome membrane to potassium ion, urea and erythritol. Lindane was the least effective agent compared with parathion, DDT, aldrin and malathion. However, the toxic effects of all of these organochlorine compounds may arise by way of modifications of the cell membrane.

Stein et al. (1981) showed that lindane (60-120 mg/kg, injected i.p.) had much the same total toxic effects on Wistar rats as PTZ: it caused myoclonic and myoclonic-tonic seizures, as well as the same sort of motor deficiencies. These authors postulated that lindane (as well as α-HCH), like PTZ, acts by interfering with the neurotransmitter effects of γ-aminobutyric acid (GABA).

To study the convulsive properties of lindane, Hulth et al. (1978) treated adult female NMRI mice with 20-50 mg/kg lindane (orally or i.p.).

At a lindane dose of 20 mg/kg, the PTZ-induced convulsive threshold was initially (up to 24 hours after treatment) lowered while 1-2 days after treatment the threshold was increased above normal and was accompanied by elevated levels of GABA in the brain. The smallest single oral dose of lindane lowering the convulsive threshold for PTZ (aftec 3 hours) corresponded to a lindane concentration of 56 μg/ℓ in whole blood. None of the lindane metabolites had any effect on the PTZ convulsive threshold, suggesting that lindane acted to cause these neural effects as the original parent compound rather than through any of its metabolites.

These studies suggest two possible means whereby lindane and other HCH isomers cause neurotoxicity: 1) by direct interaction with the neural cell membranes, and 2) by having some effect on the concentration of the neurotransmission inhibitor, GABA. Another possible effect might be postulated on the basis of the work of Dikshith et al. (1978a) who found that oral treatment of rats with 17.6 mg/kg/day lindane for 90 days caused a 38% decrease in the level of brain acetylcholinesterase. Since acetylcholinesterase is necessary for neurotransmission, a decrease may give rise to neurotoxicity.

A much more recent report suggests another possible explanation for the effects of lindane on the nervous system at acute toxic doses. Aldegunde et al. (1983) treated female Wistar rats with oral doses (by intubation) of lindane (180 and 240 mg/kg dissolved in olive oil) that resulted in convulsions. Ten minutes after administration of the higher dose, a significant increase was noted in the levels of serotonin in the brain (administration of the lower dose only caused an insignificant rise in the levels of serotonin at that time). At both doses, the level of serotonin increased 60 minutes after administration (from 0.69-0.81 μg/g brain). Levels of brain 5-hydroxyindoleacetic acid (5-HIAA) also increased. Since serotonin treatment is known to cause marked CNS actions, the convulsive effects caused by acute treatment of animals with lindane might involve increases in the levels of serotonin and metabolites of 5-hydroxytryptamine such as 5-HIAA.

Liver Toxicity

In Chapter V, it was shown that lindane and other HCH isomers cause increases in liver growth with an accompanying necrotic effect on some of the liver tissue. The effects of lindane on the subcellular composition of the hepatocytes (liver cells) were reported by several investigators.

Carevic (1977) reported that treatment of rats with lindane (40 mg/kg injected i.p.: the LD_{50} level in the rat) caused extensive liver necrosis 24 hours after treatment and resulted in vast increases of acid phosphatase, β-glucosidase and cathepsin D from the liver cell lysosomes within 1 hour of administration. The liver necrosis observed in rats after administration of lindane was attributed to labilization of the lysosomes in the liver cells. This also suggests that lindane-induced liver damage may be part of its acute toxicity. *In vitro* studies by these authors, using cell fractions rich in lysosomes, showed that 10^{-5} to 10^{-3} M lindane also caused release of lysosomal enzymes. Carevic (1977) postulated that lindane caused an increased instability of the lysosomal membrane which gave rise to release of the cytotoxic lysosomal enzymes. In a later work, Carevic (1979) found that D-penicillamine (800 mg/kg, orally) protected rat liver lysosomes from the labilizing effect of lindane (40 mg/kg), thereby protecting the liver against γ-HCH-produced cell necrosis. Decreases in the levels of total acid phosphatase were found by Mikol et al. (1980) after treatment of rats with i.p. injections of lindane in doses of 20 mg/kg/day for 3 days. Oral treatment with up to 12 mg/kg bw (240 ppm in the diet: 20% of the LD_{50}) for 4 weeks caused no such effect on this lysosomal enzyme.

Liver damage caused by lindane is also associated with effects on enzymes other than lysosomes. Dikshith et al. (1978a) reported decreases in the levels of alkaline phosphatase, succinic dehydrogenase and ATPase following oral administration of lindane (17.6 mg/kg/day) for 90 days in rats. The levels of these enzymes increased in the testis (including the lysosomal acid phosphatase) suggesting a mechanism of lysosomal labilization for the toxicity of lindane in the testis. Tiwari et al. (1982a) also found that treatment of rats with lindane at a dose of 20 mg/kg bw/day for 15 days caused marked growth retardation with associated reductions in liver levels of succinic dehydrogenase, Mg^{++}-ATPase and glucose-6-phosphatase. The presence of L-ascorbic acid (200 mg/kg bw/day) neutralized the effects of lindane on these factors. In addition, lindane treatment resulted in a decrease of liver cell membrane NADH-dehydrogenase and an increase of membrane 5'-nucleotidase (these effects were also neutralized by ascorbic acid). These results support the findings of Tiwari et al. (1982a) indicating that HCH affects the cell membrane.

After 2 months of exposure of 65 mg lindane/kg bw (500 ppm in the diet) t-HCH, the relative amounts of serum and liver lactic dehydrogenase isoenzymes in mice were found to be altered (Thakore et al., 1981a). Disc electrophoresis revealed gradual decreases in the activity of faster moving isoenzymes as compared with controls. Liver tumors showed almost complete loss of these faster moving isoenzymes. This effect persisted even after the appearance of liver tumors. While it appears that liver damage is associated with certain specific changes in liver enzyme composition and levels, it still remains to be determined whether these effects are a part of the mechanism causing liver damage or whether they are simply reflections of the liver damage.

Seifert et al. (1978) compared the biosynthesis of cytidine nucleotides in intact and regenerating liver from male Wistar rats. The experimental groups (4 animals each) consisted of rats receiving partial hepatectomy plus olive oil, partial hepatectomy plus 100 mg/kg α-HCH in olive oil, sham-operated plus olive oil, and sham-operated plus 100 mg/kg α-HCH in olive oil. The olive oil and α-HCH were administered orally. Following repeated administration, the utilization of radiolabeled orotic acid for the synthesis of cytidine nucleotides was suppressed in α-HCH-treated rats. While the uptake of cytidine and uridine and their incorporation into RNA cytosine and RNA uracil, respectively, were increased after α-HCH administration, the utilization of uridine for the synthesis of cytidine nucleotides and RNA cytosine was suppressed. Seifert et al. (1978) concluded that the results support the view that in the liver, alterations in the biosynthesis and disposition of cytidine nucleotides are connected with MFO induction rather than growth activation. Induction of the drug-metabolizing microsomal enzyme system is not necessarily associated with activation of liver growth.

Since the threshold values for effect on rat liver enzymes are greater for the pentachlorocyclohexene (30-43 μmoles/kg/day) than for the parent α-HCH (1.0-1.7 μmoles/kg/day), Parzefall et al. (1980) postulated that the liver growth enhancing activity of α-HCH is not mediated by way of the cyclohexene derivative metabolite. The noninvolvement of HCH metabolites in liver toxicity therefore agrees with the inactivity of these metabolites in causing neurotoxic effects as described earlier by Hulth et al. (1978). Future investigation may demonstrate that lindane and other HCH isomers exert most of their effects by way of the parent compound and not by way of metabolites and that metabolism of these compounds is, at least in some cases, part of a detoxification process.

In summary, the hepatotoxic effects of lindane and other HCH isomers may be due to their effects on hepatic lysosomes, lysosomal enzymes, or other liver enzymes. The liver cell growth induced by the α-HCH isomer might be due to increased uptake of RNA precursors into liver cells induced by the isomer.

Immunotoxicity

In Chapter V (see Effects on the Immune System Section under Chronic Toxicity), the immunosuppressive effects of lindane on the immune system of animals were described (Desi et al., 1978; Dewan et al., 1980). No such effects have been found in humans with the exception of one study on human lymphocytes (Roux et al., 1979) described in Chapter VI (see Blood Dyscrasias Section under Chronic Effects). The following studies may shed some light on the mechanism of the immunosuppressive effect of lindane.

Lindane and δ-HCH sharply decreased the stimulatory effect of mitogens such as phytohemagglutinin (PHA) on bovine lymphocytes, while α-HCH increased PHA-induced mitogenesis of lymphocytes, and β-HCH had no effect (Kensler and Mueller, 1978). None of the isomers of HCH (at 0.01 mM) were mitogenic in the absence of PHA. Kwong and Mueller (1979) showed that lindane antagonized the mitogenic effects of concanavalin A (conA), probably by a mechanism involving dispersion of conA-receptor complexes across the surface of the lymphocyte, thereby inhibiting the capping of these receptor-mitogen complexes that is involved in lymphocyte mitogenesis; other HCH isomers had no effect. In their study showing that lindane treatment severely decreased the mitogenic effect of PHA on human lymphocytes, Roux et al. (1979) attributed the effect to the action of lindane on lymphocyte cell membranes. Roux et al. (1978) postulated that the effect of lindane at the cell membrane level was responsible for suppressing mouse peritoneal macrophages treated with lindane at a concentration of 10^{-4} M. Such treatment caused an inhibition of uridine incorporation into macrophage RNA and was also associated with a sharply reduced intracellular pool of uridine. Lindane could have perturbed the cellular membranes so as to disrupt uridine (and other nutrient and precursor) transport as well as fusions of pinosomal and lysosomal membranes. In addition to the finding of a dose-related reduction in the formation of RNA in lindane-treated lymphocytes, there is also a report of decreased DNA formation (and some DNA damage) as demonstrated by measurement of DNA repair induction in rat thymocytes (Rocchi et al., 1980).

Thus, immunotoxic effects of lindane in mammals could be due to the severe effects of lindane on the cell membrane of immune system cells. There might be more direct damaging effects on thymocyte DNA as well.

Hematologic Effects

As noted in Chapter VI, there have been allegations of blood dyscrasias including anemias induced by lindane exposure in humans, although these allegations have been contested by some investigators.

To understand the nature of such anemia, Nichol et al. (1981) studied the accumulation of protoporphyrin and coproporphyrin in bones of sheep whose bones fluoresced pink under ultraviolet light and whose fat contained 1,2,4-trichlorobenzene. Lindane was widely used in the area as a pesticide. In the course of this study, a tissue culture study was made of chick embryo liver cells to determine the effect of lindane on porphyrin accumulation. Following treatment with lindane at a level of 5 μg/mℓ for 20 hours, the level of porphyrin (protoporphyrin plus coproporphyrin) sharply increased to 270 picomole/mg protein compared with 32 picomole/mg protein in the controls. Porphyrin is an intermediate in the biosynthesis of heme. Blockage of the biosynthetic pathway results in the accumulation of intermediate compounds that may be manifested by neurologic, dermatologic and hematologic (including anemia) symptoms (Collins et al., 1982). From the results presented, it appears that the anemia induced by lindane may have resulted from interference in the formation of hemoglobin.

Carcinogenicity

There is some evidence that lindane acts as a promoter of carcinogenic activity because of its effect on drug-metabolizing enzymes. Mikol and Decloitre (1979) showed that binding of the carcinogen benzo(a)pyrene (BaP) to rat liver DNA was enhanced by previous oral treatment of the rats with lindane in a dose as low as 1.2 mg/kg bw (24 ppm in the diet). The BaP bound to DNA in the form of the dihydrodiol derivative formed in the liver by action of aryl hydrocarbon hydroxylase (AHH). This AHH enhancing activity by lindane is very similar to the activity of phenobarbital. Decloitre and Hamon (1980) found that lindane increased the ability of liver S9 fractions (microsomes) obtained from Sprague-Dawley rats and Swiss mice to metabolize aflatoxin B1 into mutagenic (Ames test positive) derivatives. The rats and mice were given diets having 125 ppm (6.25 and 16.25 mg/kg bw for rats and mice, respectively) of lindane for 2-4 weeks, the S9 fractions were isolated from their livers; the capacity of these S9 fractions to enhance aflatoxin metabolism was compared with control untreated animal liver S9 fractions. When S9 fractions from untreated animals were used, there were 127 Salmonella revertants (per 10^8 survivors) in rats and 17 in mice, compared with 213 and 28 for rats and mice, respectively, when the S9 fractions from lindane-treated animals were used. Thus, lindane appears to enhance the metabolic activation of the carcinogen, aflatoxin, thereby enhancing its mutagenic activity, suggesting a stimulating effect on MFO enzymes.

There is also some evidence that lindane promotes carcinogenic activity by stimulating cell division. Pereira et al. (1982), for example, showed that the formation of precancerous foci in rat livers was negligible if the rats were treated with lindane (3.8 mg/kg bw: 76 ppm orally) alone. However, if the rats were treated first with the tumor initiator diethylnitrosamine (0.3 mmole/kg in water by gavage), and then given lindane, the number of such precancerous foci (i.e., γ-glutamyltranspeptidase-positive foci) increased. This suggests that lindane acts to promote the carcinogenicity of diethylnitrosamine perhaps by way of a hyperplasia induced as a regenerative response to lindane-induced liver cytotoxicity.

To determine if lindane acts directly on genetic material by formation of adducts, Saglesdorff et al. (1983) measured covalent binding to DNA in mice. Groups of young male NMRI, CF1 and C6B3F$_1$ mice were treated by gavage with a single dose of γ(^{3}H)HCH then sacrificed after 10 hours, 1, 2, 5 or 10 days. The covalent binding index was very low in all strains and could not be related to strain differences in susceptibility to tumor formation.

On the other hand, as discussed in Chapter V, it was concluded that lindane does have weak mutagenic activity. If this is true then lindane could initiate tumorigenesis through direct reaction with DNA.

Overall, there is some evidence that lindane may instigate carcinogenic activity both by epigenetic mechanisms as well as by direct action on DNA. The primary mechanism of action, however, must remain speculative until further research has been done.

Summary

The toxic effects of lindane and its isomers may be mediated by way of various effects at the cell membrane level of affected cells and may also be accompanied by effects on the activities of certain key enzymes, including enhancement of the activity of MFOs, which can then metabolize and thereby activate other toxicants including those agents known to be initiating carcinogens.

With respect to carcinogenicity, lindane may act as a promoter by causing increased cell growth (hyperplasia), or by MFO induction, thereby promoting the metabolism of other agents to proximate carcinogens. On the other hand, evidence has been presented in Chapter V suggesting that lindane may have weak mutagenic activity. If this is true, it can act as an initiator. Further studies are required to clarify its activity with respect to carcinogenesis.

Neurological effects of HCH are attributed to membrane-focused enhancing effects on nerve cell permeabilities to various solutes and to the enhancing effects on the concentration of the neurotransmitter inhibitor, GABA. Liver damage caused by HCH results from damage of the lysosomal membranes causing loss of lysosomal stability resulting in release of degradative lysosomal enzymes and may be associated with effects on nonlysosomal enzymes. Enhancement of liver growth by HCH may be due to increased membrane permeability to RNA precursors. Immunotoxic effects of lindane may be caused by interaction with the membranes of lymphocytes resulting in loss of ability of the membranes to interact with antigens, lectins and other lymphocyte stimulators. Lindane-induced degenerative changes in the testes and birth abnormalities may be caused by chromosomal damage in testicular cells.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an acceptable daily intake (ADI) is calculated. An adjusted acceptable daily intake (AADI) and health advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (body weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking water volume in } \ell\text{/day}} = \text{mg/}\ell$$

where: NOAEL = no-observed-adverse-effect level

LOAEL = lowest-observed-adverse-effect level

Body weight = 70 kg for adult or 10 kg for child

Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children

Uncertainty/Safety Factor = 10, 100 or 1000

Utilizing these equations, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1-4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1-2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivities to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977, 1980) are typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.
- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data identify a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines (NRC, 1977) for selection of an uncertainty factor, but must be considered, include the following: 1) the quality of the toxicology data, 2) the significance of the adverse effect, and 3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (and there is insufficient evidence to classify lindane as a carcinogen following oral exposure), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as 1) incomplete knowledge concerning the health effects of contaminants in drinking water, 2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results, and 3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Toxic Effects

Definitive evidence has been presented indicating that lindane is a neurotoxic agent in humans. During acute human exposures in which severe nervous system effects such as coma and seizures occur, the serum concentration of lindane may vary from 206-600 μg/ℓ (Davies et al., 1983; Munk and Mantel, 1977; Telch and Jarvis, 1982). Since blood samples are usually unavailable immediately after exposure and the elimination rate for lindane in humans has not been accurately determined, peak concentrations are uncertain. Available human studies have also failed to provide suitable data on threshold levels. Based on the data available, it is not practical to derive an AADI based on human exposure studies.

The principal effects of acute exposure of animals to lindane are neurological and behavioral. The single dose oral LD_{50} has been shown to vary from a high of 1000 mg/kg bw in mice (Wolfe and Esher, 1980) to 840 mg/kg in adult humans (Engst et al., 1979), 400 mg/kg in pigeons (Blakley 1982), 180 mg/kg in children (Engst et al., 1979), 125 mg/kg in rats (Farkas et al., 1976) and 60 mg/kg in rabbits (Desi et al., 1978).

Short-term (2-week) to subchronic (~90-day) exposures have resulted in a variety of reported effects. Müller et al. (1981) reported a decrease in motor conduction velocity in the tail nerve of rats fed lindane in the diet for 30 days at doses of 25.4 but not 12.3 or 1.3 mg/kg bw. Dallemagne et al. (1950) reported degeneration of nerve cells in dogs given a total dose of 130 or 475 mg/kg over a 7- to 44-day period. Unfortunately a NOEL could not be determined from this study. Desi (1974) reported that exposure of rats for up to 40 days resulted in an increased number of errors in maze running at doses of 5 mg/kg bw/day but not at 2.5 mg/kg. In the same study, the rate of responding in an operant conditioning test was increased even at 2.5 mg/kg. If the number of errors but not response rate is considered a detrimental effect, then a NOAEL of 2.5 mg/kg bw can be established from this experiment.

Palmer et al. (1978a) reported no teratogenic effects in rabbits fed lindane at doses up to 15 mg/kg during the critical period of gestation. In similar studies, Khera et al. (1979) fed rats as much as 25 mg/kg/day with negative results. In a 3-generation study, no adverse reproductive effects were noted in rats fed daily doses of 5 mg/kg (Palmer et al., 1978b). The lowest dose resulting in positive effects upon reproductive endpoints was reported by Dzierzawski (1977). A significant increase in resorbed fetuses was seen in hamsters treated with a single 20 mg/kg dose of lindane during the critical period of gestation. Since the effects were nonteratogenic, and since effects could not be seen by other investigators at even lower dosages using other species, 20 mg/kg was considered to be near the NOAEL.

Lindane has been shown to induce increases in levels of xenobiotic metabolizing enzymes in the liver in several studies. Lowy et al. (1977) reported increases in several liver enzymes in rats fed $\geq$20 ppm lindane in the diet. RCC (1983) reported increases in cytochrome P-450 in livers of female rats fed 0.8 ppm or more in the diet. Plass et al. (1981) stimulated increases in xenobiotic metabolizing enzymes in Wistar rats treated with $\geq$7.5 mg/kg bw on 3 consecutive days. Increases in detoxifying enzyme systems, however, are generally considered an adaptive response and not toxic manifestations unless accompanied by organ pathology.

Several subchronic and chronic studies have been conducted using mice, rats and dogs. In the RCC (1983) study both male and female rats of the KFM-HAN (outbred) SPF strain were fed 99.85% pure lindane in the diet at levels of 0, 0.2, 0.8, 4, 20 and 100 ppm for 84 consecutive days. Liver hypertrophy, kidney tubular degeneration, hyaline droplets, tubular casts, tubular distension, interstitial nephritis and basophilic tubules were seen at the 20 and 100 ppm levels. Effects were rare and very mild when noted at 4 ppm. The NOAEL was therefore considered to be 4 ppm in this study. Based upon measured food consumption, the daily intake of lindane at 4 ppm was 0.29 mg/kg in males and 0.33 mg/kg in females.

Fitzhugh et al. (1950) exposed 10 Wistar rats of each sex/group to lindane at levels of 5, 10, 50, 100, 400, 800 and 1600 ppm in the diet for 2 years or longer. An increase in liver weight and a slight degree of kidney and liver damage were noted at 100 ppm but not at 50 ppm. Assuming a daily food intake equal to 5% of body weight, the NOAEL would equal 2.5 mg/kg/day.

Wolfe and Esher (1980) exposed two species of wild mice to 200 ppm lindane in the diet for 8 months with no reported effects on food consumption, growth rate, mortality, reproduction or behavior. Weisse and Herbst (1977) exposed SPF mice to 12.5, 25 or 50 ppm lindane in the diet for 80 weeks and reported no fine structural hepatocellular alterations. Since no effects were reported in these two studies, a maximum NOAEL cannot be determined. The mouse is evidently one of the more resistant species since acute LD_{50} doses were also high in mice.

Lehman (1965) fed dogs, 2 animals/sex/group, 0 or 15 ppm lindane in the diet for 63 weeks. No differences were noted for food consumption, hematological or histopathological parameters. Rivett et al. (1978) exposed four beagle dogs/sex/group to 0, 25, 50 or 100 ppm lindane in the diet for 2 years. The daily intake of lindane based on measured food consumption was 0.83, 1.60 and 2.92 mg/kg bw for the low, medium and high dose. No effects were reported for the 25 and 50 ppm groups. At 100 ppm serum alkaline phosphatase was significantly increased and the livers were dark, friable and greatly enlarged. The NOAEL was considered to be 50 ppm (1.60 mg/kg bw) in this study.

Quantification of Noncarcinogenic Effects

Existing Criteria and Standards. The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted a threshold limit value-time weighted average (TLV-TWA) of 0.5 mg/m³ and a TLV short-term (15 minutes) exposure limit (STEL) of 1.5 mg/m³ (NRC, 1982). OSHA (1976) has established a standard for airborne contaminants which require that an employee's exposure to lindane not exceed an 8-hour TWA of 0.5 mg/m³ in any 8-hour work shift of a 40-hour week. WHO/FAO tentatively proposed a human ADI of 0.001 mg/kg bw (0.07 mg/day for a 70 kg man) (NRC, 1977).

A maximum contaminant level of 0.004 mg/ℓ for lindane in drinking water was promulgated in 1975 as an interim standard by the U.S. EPA (Federal Register, 1975). This interim standard is based upon a NOEL of 15 ppm (0.3 mg/kg) in dogs fed lindane daily for up to 63 weeks (Lehman, 1965). The calculations were based upon a 500-fold safety factor and the assumption that 20% of total intake is by drinking water. The WHO (1984) has recommended a drinking water criterion of 3 μg lindane/ℓ.

Tolerances for residues of lindane established by the OPP (40 CFR, 1982) in or on raw agricultural commodities are given below:

- 7 ppm in or on the fat of meat from cattle, goats, horses and sheep
- 4 ppm in or on the fat of meat from hogs
- 3 ppm in or on cucumbers, lettuce, melons, mushrooms, pumpkins, squash, summer squash and tomatoes
- 1 ppm in or on apples, apricots, asparagus, avocados, broccoli, brussel sprouts, cabbage, cauliflower, celery, cherries, collards, eggplants, grapes, guavas, kale, kohlrabi, mangoes, mustard greens, nectarines, okra, onions (dry bulb only), peaches, pears, peppers, pineapples, plums (fresh prunes), quinces, spinach, strawberries and Swiss chard.

Development of HAs. The availability of short-term studies for the development of 1-day and 10-day HAs are very limited. For exposures of <1 week duration, the lowest dosage causing detrimental effects was reported by Dzierzawski (1977). However, this study is not considered appropriate to derive a 1-day HA. In this study, there was observed increased resorption of fetuses and retarded development in pregnant hamsters given a single dose of 20 mg/kg lindane.

For a 10-day HA, the study by Müller et al. (1981) in which decreased motor conduction velocity was detected in the tail nerve of rats fed lindane for 30 days at 25.4, but not 12.3 mg/kg, is considered suitable for the development of a 10-day HA. The 10-day HA can be developed as follows:

$$\text{10-day HA (adult)} = \frac{12.3 \text{ mg/kg/day} \times 70 \text{ kg}}{100 \times 2 \text{ ℓ/day}} = 4.3 \text{ mg/ℓ}$$

$$\text{10-day HA (child)} = \frac{12.3 \text{ mg/kg/day} \times 10 \text{ kg}}{100 \times 1 \text{ ℓ/day}} = 1.2 \text{ mg/ℓ}$$

where:

12.3 mg/kg/day = NOAEL
70 kg = weight of adult
10 kg = weight of child
2 ℓ = daily water intake, adult
1 ℓ = daily water intake, child
100 = uncertainty factor where an acceptable acute or chronic animal study is available

There are insufficient toxicological data available in the scientific literature to derive a 1-day HA. The 10-day HAs of 4.3 mg/ℓ for adults and 1.2 mg/ℓ for children derived from the study of Müller et al. (1981) are recommended.

Development of Long-Term AADIs. Three longer term studies have been conducted to date using doses spanning the toxic threshold, thus allowing a maximum NOAEL to be defined. These include the 12-week study using rats by RCC (1983), the chronic rat study of Fitzhugh et al. (1950) and the chronic dog studies by Rivett et al. (1978).

ADI -- Fitzhugh et al. (1950) exposed 10 Wistar rats of each sex to lindane at levels of 0, 5, 10, 50, 100, 400, 800 and 1600 ppm in the diet for 2 years or longer. An increase in liver weight and a slight degree of kidney and liver damage were noted at 100 ppm but not at 50 ppm. Assuming a daily food intake equal to 5% of body weight, the highest NOAEL would equal 2.5 mg/kg/day.

If the study by Fitzhugh et al. (1950) is considered to be suitable for the development of an ADI, it can be derived as follows:

$$\text{ADI} = \frac{\text{2.5 mg/kg/day} \times \text{70 kg}}{1000} = \text{0.175 mg/day}$$

where:

2.5 mg/kg/day = the largest observed NOAEL
70 kg = weight of adult human
1000 = safety factor for a study where all parameters were not evaluated

Using 0.175 mg/day as the ADI and assuming the 70 kg adult consumes 2 ℓ of drinking water per day, the AADI is calculated as follows:

$$\text{AADI} = \frac{\text{0.175 mg/day}}{2\ \ell\text{/day}} = 0.088\ \text{mg}/\ell$$

This AADI calculation assumes 100% of the human exposure to lindane is derived from drinking water. Once the tolerances for residues of lindane in various food commodity reported earlier in this section are evaluated for inclusion as a part of relative source contribution, this AADI may be modified.

Rivett et al. (1978) exposed four beagle dogs/sex/group to 0, 25, 50 or 100 ppm lindane in the diet for 2 years. The daily intake of lindane based on measured food consumption was 0.83, 1.60 and 2.92 mg/kg bw for the low, medium and high dose. No effects were reported for the 25 and 50 ppm groups. At 100 ppm, serum alkaline phosphatase was significantly increased and the livers were dark, friable and greatly enlarged. The highest NOAEL was considered to be 50 ppm (1.60 mg/kg bw) in this study.

If the study by Rivett et al. (1978) is considered suitable for the development of an ADI, it can be derived as follows:

$$\text{ADI} = \frac{1.6 \text{ mg/kg/day} \times 70 \text{ kg}}{1000} = 0.112 \text{ mg/day}$$

where:

1.6 mg/kg/day = the largest observed NOAEL
70 kg = weight of adult human
1000 = safety factor for a study where all parameters were not evaluated

Using 0.112 mg/day as the ADI and assuming the 70 kg adult consumes 2 ℓ of drinking water per day, the AADI is calculated as follows:

$$\text{AADI} = \frac{0.112 \text{ mg/day}}{2 \text{ ℓ/day}} = 0.056 \text{ mg/ℓ}$$

This AADI calculation assumes 100% of the human exposure to lindane is derived from drinking water. Once the tolerances for residues of lindane in various food commodity reported earlier in this section are evaluated for inclusion as a part of relative source contribution, this AADI may be modified.

In the RCC (1983) study both male and female rats of the KFM-HAN (outbred) SPF strain were fed pure lindane (99.85%) in the diet at levels of 0, 0.2, 0.8, 4, 20 and 100 ppm for 84 consecutive days. Liver hypertrophy, kidney tubular degeneration, hyaline droplets, tubular casts, tubular distension, interstitial nephritis and basophilic tubules were seen at the 20 and 100 ppm levels. Effects were rare and very mild when noted at 4 ppm. The highest NOAEL was therefore considered to be 4 ppm in this study. Based upon measured food consumption, the daily intake of lindane at 4 ppm was 0.29 mg/kg in males and 0.33 mg/kg in females.

If the study by RCC (1983) is considered to be suitable for the development of an ADI, it can be derived as follows:

$$\text{ADI} = \frac{0.33 \text{ mg/kg/day} \times 70 \text{ kg}}{1000} = 0.023 \text{ mg/day}$$

where:

0.33 mg/kg/day = the largest observed NOAEL
70 kg = weight of adult human
1000 = safety factor for a study of acceptable quality but significantly less than lifetime in duration

Using 0.023 mg/day as the ADI and assuming the 70 kg adult consumes 2 ℓ of drinking water per day, the AADI is calculated as follows:

$$\text{AADI} = \frac{0.023\ \text{mg/day}}{2\ \ell\text{/day}} = 0.012\ \text{mg}/\ell = 0.010\ \text{mg}/\ell$$

Recommendation. It is recommended that the AADI of 0.012 mg/ℓ based on the RCC (1983) study be considered. This study was well designed and managed. Pathological changes in the liver and kidneys were evaluated in greater detail than in the other studies.

Carcinogenic Effects

In studies using rats Fitzhugh et al. (1950) was unable to detect increases in the incidence of liver tumors following long-term exposure to as much as 1600 ppm lindane in the food. This study was compromised because not all organs were examined and in some cases only one or even no liver slices were evaluated. Truhaut (1954) also reported negative results. The maximum dose used in this study, however, was 100 ppm (5 mg/kg bw) which is less than the minimum dose causing tumors in mice. Ito et al. (1975) reported hyperplasia but no neoplasia in the livers of rats exposed up to 48 weeks to 500 ppm (25 mg/kg bw) lindane. Only small numbers of rats were reported on in each group. This study is also inconclusive since it is possible that the hyperplasia may progress to neoplasia with continued exposure.

In a study that was adequately designed and conducted, NCI (1977) reported no significant increases in the incidence of liver cancer in male or female rats fed up to 472 ppm (74 mg/kg bw) in the diet for 80 weeks. Reuber (1979), however, reported results from the same study indicating that the incidence of tumors was increased in the treated animals. His conclusions were apparently based upon a re-evaluation of the tissue sections. Since he gave no indication as to how the tissues were re-examined or why he considered the original NCI interpretation of the tissues incorrect, it is difficult to draw conclusions from this study.

In studies using mice, Didenko et al. (1973), Nagasaki et al. (1975) and Herbst et al. (1975) failed to detect increases in tumor incidence following lindane treatment. In the first two studies exposure length was only 5 and 24 weeks, respectively, making it unlikely that tumors would have developed. In the latter study, the maximum concentration used (50 ppm) was less than that required to induce tumors in the positive experiments.

Goto et al. (1972) was the first to report a positive effect of lindane in mice. Liver tumors were reported in 5 of 10 IRC-JCL male mice fed 600 ppm (~78 mg/kg bw). This experiment was compromised by the short duration and small numbers of animals per group. Hanada et al. (1973) reported that 1 of 3 surviving females and 3 of 4 surviving males developed liver tumors after 37-38 weeks exposures to 600 ppm (78 mg/kg bw) lindane compared with none in controls. While the results appear to be positive, the numbers are too small for an accurate risk assessment. In a study reported by NCI (1977) in which both male and female mice were exposed to either 80 or 160 ppm (10.4 or 20.8 mg/kg bw) lindane in the diet, a significant increase in liver tumor incidence was reported only for low dose males. As was the case with the NCI (1977) rat study, Reuber (1979) reported different results for the same experiment. For reasons mentioned previously, it is difficult to draw conclusions from this study except to state that a statistically significant increase in the incidence of hepatocellular carcinoma was reported by NCI for the low-dose males.

Thorpe and Walker (1973) exposed CF1 mice 30/sex/group to 400 ppm (52 mg/kg bw) lindane in the diet for up to 110 weeks. Liver tumors developed in 27 of 28 exposed males compared with 11 of 45 controls ($p<0.001$) and 20 of 21 exposed females compared with 10 of 44 controls. This study was compromised by the low percentage of exposed mice surviving 110 weeks, 3% of females and 17% of males. Despite this criticism, it provided the most clearcut evidence for induction of liver tumors by lindane since both group size and the number of animals with liver tumors was large.

The evidence to date indicates that lindane is carcinogenic to mice when administered orally, producing liver tumors. Positive results were not obtained in studies on rats and dogs. With the exception of the Thorpe and Walker (1973) and the NCI (1977) studies, however, the experiments on these species were generally compromised by inadequate exposure duration, small number of test animals per group, insufficient dose or incomplete evaluation of tissues.

The IARC have classified lindane in Group 3; inadequate evidence for carcinogenicity in humans, limited evidence for carcinogenicity in animals and inadequate evidence for activity in short-term tests. The U.S. EPA's Office of Pesticide Programs (U.S. EPA, 1985) has stated

> Using the new Proposed Guidelines for Carcinogen Risk Assessment (cited above), the CAG has classified lindane as "B2-C' (i.e., in between the lower half of the 'B' category of 'probable' and the

> 'C' category of 'possible' carcinogen classifications) based upon evidence that lindane gives rise to malignant liver tumors in two strains of mice, plus supportive evidence of pre-cancerous liver lesions in shorter term studies."

This weight of evidence classification also included consideration that, on the one hand, at least one study was positive in both sexes and a lindane metabolite has been shown to be oncogenic, while, on the other hand, and leaning the classification toward class "C," lindane has not been shown to be mutagenic after extensive testing and none of the oncogenicity studies showed a dose-response. Therefore, the weight of evidence appears to be closer to a Category C carcinogen than to Category B2 carcinogen.

The available data do not permit definitive decisions on the oncogenic potential of lindane in the rat. The Office of Pesticide Programs is requiring that a rat oncogenicity bioassay be performed (U.S. EPA, 1985). Until definitive decision on the oncogenic potential of lindane is established, lindane will be classified in EPA's Group C for the reasons outlined by the Office of Pesticide Programs.

There is no direct evidence that lindane causes cancer in humans. Exposure to lindane was recorded in case control studies of soft-tissue sarcomas and lymphomas (Eriksson et al., 1981; Hardell et al., 1981), but was insufficiently frequent for any conclusion to be drawn. The human evidence is therefore considered "inadequate." An overall IARC (1982) classification for lindane is group 3, indicating that carcinogenicity cannot be determined. However, the positive results in several mouse studies and the data suggesting that carcinogenic metabolites (i.e. 2,4,6-trichlorophenol) are present in mice, rats, rabbits and humans yields a stronger weight of evidence that lindane may be more carcinogenic to humans than a group 3 listing might convey.

Quantification of Carcinogenic Effects

A risk estimate was calculated based on the oncogenic effects observed in the liver of male CF1 mice fed lindane in the diet. The estimated levels that would result in increased lifetime risks at 10^{-4}, 10^{-5} and 10^{-6}, respectively, by EPA's Carcinogen Assessment Group (U.S. EPA, 1980) and NAS (1977) are given below:

	Associated Cancer Excess Lifetime Cancer Risk (μg/ℓ)		
	10^{-4}	10^{-5}	10^{-6}
CAG	2.650	0.265	0.0265
NAS	5.50	0.55	0.055

Summary

The recommended HAs and AADI are summarized in Table VIII-1.

TABLE VIII-1

Summary of QTE

Criteria	Drinking Water Concentration (mg/ℓ) 10 kg child	70 kg adult	Reference
1-day HA	Insufficient data		
10-day HA	1.2	4.3	Müller et al., 1981
AADI		0.010	RCC, 1983
Excess cancer risk levels		U.S. EPA, 1980	NAS, 1977
10^{-4}		2.65 µg/ℓ	5.50 µg/ℓ
10^{-5}		0.265 µg/ℓ	0.55 µg/ℓ
10^{-6}		0.0265 µg/ℓ	0.055 µg/ℓ

IX. REFERENCES

Abbott, D.C., R. Goulding and J.O'G. Tatton. 1968. Organochlorine pesticide residues in human fat in Great Britain. Br. Med. J. 3: 146-149.

Ahdaya, S.M., R.J. Monroe and F.E. Guthrie. 1981. Absorption and distribution of intubated insecticides in fasted mice. Pestic. Biochem. Physiol. 16(1): 38-46.

Ahmed, F.E., R.W. Hart and N.J. Lewis. 1977. Pesticide induced DNA damage and its repair in cultured human cells. Mutat. Res. 42: 161-174.

Aiyar, A.S. 1980. Biological implications of pesticides: Studies with lindane. Manage. Environ. p. 182-192.

Albert, L., F. Mendez, M.E. Cebrian and A. Portales. 1980. Organochlorine pesticide residues in human adipose tissue in Mexico: Results of a preliminary study in three Mexican cities. Arch. Environ. Health. 35(5): 262-269.

Albro, P.W. and R. Thomas. 1974. Intestinal absorption of hexachlorobenzene and hexachlorocyclohexane isomers in rats. Bull. Environ. Contam. Toxicol. 12: 289-294.

Aldegunde, M., M. Parafita and M.P. Fernandez Otero. 1983. Effect of γ-hexachlorocyclohexane on serotonin metabolism in rat brain. Gen. Pharmacol. 14(2): 303-305.

Allsup, T. and D. Walsh. 1982. Gas chromatographic analysis of chlorophenylmercapturic acid lindane metabolites. J. Chromatogr. 236(2): 421-428.

Ames, B.N., J. McCann and E. Yamasaki. 1975. Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat. Res. 31: 347-364.

Angerer, J., R. Heinrich and H. Laudehr. 1981. Occupational exposure to hexachlorocyclohexane. Int. Arch. Occup. Environ. Health. 48(4): 319-324.

Antunes-Madeira, M.C. and V.M.C. Madeira. 1979. Interaction of insecticides with lipid membranes. Biochim. Biophys. Acta. 550(3): 384-392.

Atlas, E. and C.S. Giam. 1981. Global transport of organic pollutants: Ambient concentrations in the remote marine atmosphere. Science. 211(4478): 163-165.

Baquar, S.R. and N.R. Khan. 1971. Effect of γ-hexachlorocyclohexane (HCCH) on the mitotic cells of Pisum sativum L. Rev. Biol. (Lisbon). 7: 195-202.

Bargman, H. 1982. Acute intoxication with lindane. Can. Med. Assoc. J. 127(5): 360.

Baumann, K., J. Angerer, R. Heinrich and G. Lehnert. 1980. Occupational exposure to hexachlorocyclohexane. I. Body burden of HCH-isomers. Int. Arch. Occup. Environ. Health. 47: 119-127.

Baumann, K., K. Behling, H-L. Brassow and L.K. Stape. 1981. Occupational exposure to hexachlorocyclohexane. III. Neurophysiological findings and neuromuscular function in chronically exposed workers. Int. Arch. Occup. Environ. Health. 48(2): 165-172.

Benes, V. and R. Sram. 1969. Mutagenic activity of some pesticides in Drosophila melanogaster. Ind. Med. 38: 442-444.

Bergman, K., I. Brandt, L.E. Appelgren and P. Slanina. 1981. Structure-dependent, selective localization of chlorinated xenobiotics in the cerebellum and other brain structures. Experientia. 37: 1184-1185.

Besuglyi, V.P., I.L. Odintsova and N.Z. Gorskaya. 1973. Morphological composition of blood of persons working with a complex of orkanochlorine and organophosphorus pesticides. Urach. Delo. 11: 134-138.

Blakley, B.R. 1982. Lindane toxicity in pigeons. Can. Vet. J. 23(9): 267-268.

Blevins, R.D. 1979. Organochlorine pesticides in gamebirds of Eastern Tennessee. Water Air Soil Pollut. 11: 71-75.

Brassow, H-L., K. Baumann and G. Lehnert. 1981. Occupational exposure to hexachlorocyclohexane. II. Health conditions of chronically exposed workers. Int. Arch. Occup. Environ. Health. 48: 81-87.

Bristol, D.W. 1980. Determination of chemical residues in whole blood of selected Love Canal area residents. Prepared by U.S. Health Effects Research Laboratory, Research Triangle Park, NC. EPA 600/1-80-036. NTIS PB 82-196353.

Burns, J.E. 1974. Organochlorine pesticide and polychlorinated biphenyl residues in biopsied human adipose tissue - Texas, 1969-1972. Pestic. Mon. J. 7: 122-126.

Canton, J.H., G.J. van Esch, P.A. Greve and A.B.A.M. Van Hellmond. 1977. Accumulation and elimination of α-hexachlorocyclohexane (α-HCH) by the marine algae Chlamydomonas and Dunaliella. Water Res. 11: 111-115.

Carevic, O. 1977. The effect of gamma-hexachlorocyclohexane on rat liver lysosomes. Biochem. Pharmacol. 26(15): 1377-1381.

Carevic, O. 1979. The effect of D-penicillamine on the release of acid hydrolases from rat liver lysosomes induced by gamma-hexachlorocyclohexane. Biochem. Pharmacol. 28(14): 2181-2185.

Chadwick, R.W. and J.J. Freal. 1972. The identification of five unreported lindane metabolites recovered from rat urine. Bull. Environ. Contam. Toxicol. 7: 137-146.

Chadwick, R.W., M.F. Cranmer and A.J. Peoples. 1971. Comparative stimulation of γ-HCH metabolism by pretreatment of rats with γ-HCH, DDT, and DDT plus HCH. Toxicol. Appl. Pharmacol. 18: 685-695.

Chadwick, R.W., L.T. Chuang, and K. Williams. 1975. Dehydrogenation: A previously unreported pathway of lindane metabolism in mammals. Pestic. Biochem. Physiol. 5: 575-586.

Chadwick, R.W., M.F. Copeland and C.J. Chadwick. 1978a. Enhanced pesticide metabolism: A previously unreported effect of dietary fibre in mammals. Food Cosmet. Toxicol. 16(3): 217-225.

Chadwick, R.W., J.J. Freal, G.W. Sovocool, C.C. Bryden and M.F. Copeland. 1978b. The identification of three previously unreported lindane metabolites from mammals. Chemosphere. 8: 633-640.

Chadwick, R.W., E.J. Faeder, L.C. King, M.F. Copeland, K. Williams and L.T. Chuang. 1978c. Effect of acute and chronic Cd exposure on lindane metabolism. Ecotoxicol. Environ. Safety. 2: 301-316.

Chadwick, R.W., M.F. Copeland and L. Rosenstein. 1979. The effect of Kepone exposure during gestation and lactation on the metabolism of lindane by weanling rats. Toxicol. Lett. 4: 247-252.

Chadwick, R.W., M.F. Copeland, M.L. Mole, S. Nesnow and N. Cooke. 1981. Comparative effect of pretreatment with phenobarbital, aroclor 1254, and β-naphthoflavone on the metabolism of lindane. Pestic. Biochem. Physiol. 15: 120-136.

Chand, B. and M. Ramachandran. 1980. Effect of dietary hexachlorocyclohexane on certain biochemical changes in rats. Ind. J. Exp. Biol. 18: 735-736.

Chen, C.P. 1968. The effects of protein deficient diet on the acute toxicity of lindane. M.S. Thesis, Queens Univ., Kingston, Ontario, Canada.

Clark, D.E., H.E. Smalley, H.R. Crookshank and F.M. Farr. 1974. Chlorinated hydrocarbon insecticide residues in feed and carcasses of feedlot cattle, Texas-1972. Pestic. Monit. J. 8: 180-183.

Cohen, J.M. and C. Pinkerton. 1966. Widespread translocation of pesticides by air transport and rain-out. Adv. Chem. Ser. 60: 163.

Collins, A.G., A.W. Nichol and S. Elsbury. 1982. Porphyria cutanea tarda and agricultural pesticides. Aust. J. Dermatol. 23(2): 70-75.

Crissman, J.W. 1980. Lindane intoxication in man. J. Am. Vet. Med. Assoc. 177(4): 312-313.

Crosby, D.G. 1978. Atmospheric transport and transformation of pesticides. In: Symposium on Environmental Transport and Transformation of Pesticides: Joint U.S.-USSR Project 02.03-31. Forms and Mechanisms by Which Pesticides and Chemicals are Transported. NTIS PB-280714, p. 1-3.

Dale, W.E., M.F. Copeland and W.J. Hayes. 1965. Chlorinated insecticides in the body fat of people in India. Bull. WHO 33: 471-477.

Dallemagne, M.J., M.A. Gerebtzoff and E. Phillppot. 1950. Fat overloading of the body during chronic intoxication of the dog with γhexachlorocyclohexane. Experientia. 6: 274.

Davies, J.E., H.V. Dedhia, C. Morgade, A. Barquet and H.I. Maibach. 1983. Lindane poisonings. Arch. Dermatol. 119(2): 142-144.

DeBrabander, M., R. Van deVeire, F. Aerts, S. Geuens and J. Hoebeke. 1976. A new culture model facilitating rapid quantitative testing of mitotic spindle inhibition in mammalian cells. J. Natl. Cancer Inst. 56: 357-363.

Decloitre, F. and G. Hamon. 1980. Species-dependent effects of dietary lindane and/or zineb on the activation of aflatoxin B_1 into mutagenic derivatives. Mutat. Res. 79(3): 185-192.

Demozay, D. and G. Marechal. 1972. B. Physical and chemical properties. In: Lindane, Monograph of an Insecticide, E. Ulmann, Ed. V.K. Schillinger Publ., Freiburg im Breisgaw. p. 15-18.

Desi, I. 1974. Neurotoxicological effect of small quantities of lindane. Int. Arch. Arbeitsmed. 33: 153-162.

Desi, I., L. Varga and I. Farkas. 1978. Studies on the immunosuppressive effect of organochlorine and organophosphoric pesticides in subacute experiments. J. Hyg. Epidemiol. Microbiol. Immunol. (Praha). 22(1): 115-122.

Desi, J., G. Dura and J. Szlobodnyik. 1977. Testing of pesticide toxicity in tissue culture. J. Toxicol. Environ. Health. 2: 1053-1066.

Dewan, A., S.K. Gupta, J.P. Jani and S.K. Kashyap. 1980. Effect of lindane on antibody response to typhoid vaccine in weanling rats. J. Environ. Sci. Health [B]. 15(4): 395-402.

Didenko, G.G., O.V. Chernov and T.D. Gupalovitch. 1973. Investigations of the possible carcinogenic action of the gamma-isomer of hexachlorocyclohexane. Gig. Sanit. 38: 98-99.

Dikshith, T.S.S., S.K. Tandon, K.K. Datta, P.K. Gupta and J.R. Behari. 1978a. Comparative response of male rats to parathion and lindane: Histopathological and biochemical studies. Environ. Res. 17(1): 1-9.

Dikshith, T.S.S., K.K. Datta, H.S. Kushwah and R.B. Raizada. 1978b. Histopathological and biochemical changes in guinea pigs after repeated dermal exposure to benzene hexachloride. Toxicology. 10(1): 55-66.

Dillon, J.C., G.B. Martin and H.T. O'Brien. 1981. Pesticide residues in human milk. Food Cosmet. Toxicol. 19: 437-442.

Dzierzawski, A. 1977. Embryotoxicity studies of lindane in the golden hamster, rat and rabbit. Bull. Vet. Inst. Pulawy. 21(3-4): 85-93.

Earl, F.L., E.J. Van Loon, B.E. Melveger, J.E. Reinwall, G.W. Bierbower, R. Kass and W. Miguez. 1970. Lindane toxicity. A comparative study in dogs and miniature swine with and without phenobarbital. Toxicol. Appl. Pharmacol (Abstr). 17: 287.

Eidmann, H.H., O. Bergman, B. Henningsson and C. Moller. 1979. DDT and lindane residues on treated conifer seedlings and in soil. Ambio. 8(5): 214-217.

El Beit, I.O.D., J.V. Wheelock and D.E. Cotton. 1981a. Factors affecting soil residues of dieldrin, endosulfan, γ-HCH, dimethoate, and pyrolan. Ecotoxicol. Environ. Safety. 5(2): 135-160.

El Beit, I.O.D., J.V. Wheelock and D.E. Cotton. 1981b. Factors involved in the dynamics of pesticides in soils -- The effect of temperature and period of contact on leachability and adsorption of pesticides by soils. Int. J. Environ. Stud. 16(3-4): 189-196.

Engst, R., R. Macholz, M. Kujawa, H.J. Lewerenz and R. Plass. 1976. The metabolism of lindane and its metabolites gamma-2,3,4,5,6-pentachlorocyclohexene, pentachlorobenzene, and pentachlorophenol in rats and the pathways of lindane metabolism. J. Environ. Sci. Health [B]. 11(2): 95-117.

Engst, R., R.M. Macholz and M. Kujawa. 1979. Metabolism of lindane in microbial organisms, warm-blooded animals and humans. Gig. Sanit. 10: 64-65.

Eriksson, M., L. Hardell, N.O. Berg, T. Möller and O. Axelson. 1981. Soft-tissue sarcomas and exposure to chemical substances: A case-referent study. Br. J. Ind. Med. 38: 27-33.

Esaac, E.G. and F. Matsumura. 1980. Metabolism of insecticides by reductive systems. Pharmacol. Ther. Part A 9(1): 1-26.

Fagan, J.E. 1981. Henoch-Schonlein purpura and γ-benzene hexachloride. Pediatrics. 67(2): 310-311.

FAO/WHO (Food and Agricultural Organization/World Health Organization) Food Standards Programme. 1974. Recommended International Maximum Limits for Pesticide Residues: 4th Ser.

Federal Register. 1975. Part 141-National Interim Primary Drinking Water Regulations. Subpart 141.12. Maximum contaminant levels for organic chemicals. 40: 59570-59571.

Farkas, I., I. Desi and G. Dura. 1976. Differences in the acute and chronic neurotoxic effects of chlorinated hydrocarbon, organophosphate and carbamate pesticides. Adverse Eff. Environ. Chem. Psychotropic Drugs. 2: 201-213.

Fitzhugh, O.G., A.A. Nelson and J.P. Frawley. 1950. The chronic toxicities of technical benzene hexachloride, and its alpha, beta, and gamma isomers. J. Pharmacol. Exp. Ther. 100: 59-66.

Fitzloff, J.F., J. Portig and K. Stein. 1982. Lindane metabolism by human and rat liver microsomes. Xenobiotica. 12(3): 197-202.

Foster, T.S. and J.G. Saha. 1978. The in vitro metabolism of lindane by an enzyme preparation from chicken liver. J. Environ. Sci. Health. B13(1): 25-45.

Fouts, T. and R.H. Adamson. 1959. Drug metabolism in the newborn rabbit. Science. 129: 897-898.

Frawley, J.P. and O.G. Fitzhugh. 1949. Rate of disappearance of isomers of benzene hexachloride from fat deposits in rats. Fed. Proc. 8: 292-293.

Freal, J.J. and R.W. Chadwick. 1973. Metabolism of hexachlorocyclohexane to chlorophenols and effect of isomer pretreatment on lindane metabolism in rat. J. Agric. Food Chem. 21: 424-427.

Frear, D.S. and J.J. Menn. 1978. Pesticide transport and transformation in plants. In: Symposium on Environmental Transport and Transformation of Pesticides: Joint U.S.-USSR Project 02.03-31. Forms and mechanisms by which pesticides and chemicals are transported. NTIS PB-280714, p. 126-139.

Fuhremann, T.W. and E.P. Lichtenstein. 1980. A comparative study of persistence, movement, and metabolism of six carbon-14 insecticides in soils and plants. J. Agric. Food Chem. 28(2): 446-452.

Gabridge, M.G. and M.S. Legator. 1969. Host-mediated microbial assay for the detection of mutagenic compounds. Proc. Soc. Exptl. Biol. Med. 130: 831-834.

Gaines, T.B. 1969. Acute toxicity of pesticides. Toxicol. Appl. Pharmacol. 14: 515-534.

Geyer, H., A.G. Kraus and W. Klein. 1980. Relationship between water solubility and bioaccumulation potential of organic chemicals in rats. Chemosphere. 9: 277-291.

Ginsburg, C.M., W. Lowry and J.S. Reisch. 1977. Absorption of lindane (gamma benzene hexachloride) in infants and children. J. Pediatrics. 91(6): 998-1000.

Gopalaswamy, U.V., M.P. Phondke and A.S. Aiyar. 1980. Biotransformation of lindane in mammals and its significance for safety assessment of the pesticide. In: Proc. Symposium on Isotope and Radiation Research on Animal Diseases and their Vectors, Vienna, May 7-11, 1979. p. 233-246.

Goto, M., M. Hattori and T. Mizagawa. 1972. Contributions to ecology. II. Hepatoma development in mire after administration of HCH isomers in high dosages. Chemosphere. 1: 279-282.

Grasselli, J.G. and W.M. Ritchey, Ed. 1975. CRC Atlas of Spectral Data and Physical Constants for Organic Compounds, 2nd ed., Vol. III. Chemical Rubber Co., Cleveland, OH. p. 111-112.

Gunther, F.A., W.E. Westlake and P.S. Jaglan. 1968. Reported solubilities of 738 pesticide chemicals in water. Res. Rev. 20: 1-145.

Gupta, S.K., N. Srivastava, J.S. Patel, S.K. Chatterjee and S.K. Kashyap. 1980. Organochlorine insecticide residues in fat of people from urban centres in India-1. Pesticides. 14(6): 3-4, 13.

Gupta, S.K., J.R. Parikh, M.P. Shah, S.K. Chatterjee and S.K. Kashyap. 1982. Changes in serum hexachlorocyclohexane (HCH) residues in malaria spraymen after short-term occupational exposure. Arch. Environ. Health. 37(1): 41-44.

Haider, K. 1979. Degradation and metabolization of lindane and other hexachlorocyclohexane isomers by anaerobic and aerobic soil microorganisms. Z. Naturforsch. Teil C. 34(11): 1066-1069.

Hamada, M., E. Kawano, S. Kawamura and M. Shiro. 1981. Radiation- and photo-induced degradation of five isomers of 1,2,3,4,5,6-hexachlorocyclohexane. Agric. Biol. Chem. 45(3): 659-665.

Hamelink, J.L. and R.C. Waybrant. 1976. DDE and lindane in a large-scale model lentic ecosystem. Trans. Am. Fish. Soc. 105: 124-134.

Hanada, M., C. Yutani and T. Miyaji. 1973. Induction of hepatoma in mice by benzene hexachloride. Gann. 64: 511-513.

Hansch, C. and A.J. Leo. 1979. Substituent Constants for Correlation Analysis in Chemistry and Biology. Wiley-Interscience, NY.

Hansen, P.D. 1980. Uptake and transfer of the chlorinated hydrocarbon lindane (γ-BHC) in a laboratory freshwater food chain. Environ. Pollut. (Series A). 21(2): 97-108.

Hardell, L., M Eriksson, P. Lenner and E. Lundgren. 1981. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case control study. Br. J. Cancer. 43: 169-176.

Harrison, M.A., T.J. Nicholls and C.G. Rousseaux. 1980. Lindane toxicity in lambs. Australian Vet. J. 56(1): 42.

Herbst, M. and G. Bodenstein. 1972. Toxicology of lindane. In: Lindane, E. Ulmann, Ed. Verlag K. Schillinger Publ., Freiburg im Breisgaw. p. 23-82.

Herbst, M., J. Guenard, H. Köllmer and H. Stötzer. 1974. Enzyme induction in the liver following administration of lindane by the oral route: A functional and morphological study in rats. Arch. Toxicol. 32: 115-130.

Herbst, M., I. Weisse and H. Koellmer. 1975. Contribution to the question of the possible hepatocarcinogenic effects of lindane (gamma benzene hexachloride). Toxicology. 4: 91-96.

Heritace, A.D. and I.C. MacRae. 1979. Degradation of Hexachlorocyclohexanes and structurally related substances by clostridium sphenside. Aust. J. Biol. Sci. 32: 493-500.

Hoffman, D.J. and W.C. Eastin. 1982. Effects of lindane, paraquat, toxaphene, and 2,4,5-trichlorophenoxyacetic acid on mallard embryo development. Arch. Environ. Contam. Toxicol. 11(1): 79-86.

Hollstein, M., J. McCann, F.A. Angelosanto and N.W. Nichols. 1979. Short-term tests for carcinogens and mutagens. Mutat. Res. 65: 133-226.

Hooker Chemical Corporation. 1969. FBHC, Fortified Benzene Hexachloride, Bulletin No. 480, Industrial Chemicals Division, Niagara Falls, NY, p. 1-4.

Hosler, J., C. Tschanz, C.E. Hignite and D.L. Azarnoff. 1979. Topical application of lindane cream (Kwell) and antipyrine metabolism. J. Invest. Dermatol. 74: 51-53.

Hulth, L., L. Hoglund, A. Bergman and L. Moller. 1978. Convulsive properties of lindane, lindane metabolites and the lindane isomer α-hexachlorocyclohexane: Effects on the convulsive threshold for pentylenetetrazol and the brain content of γ-aminobutyric acid (GABA) in the mouse. Toxicol. Appl. Pharmacol. 46(1): 101-108.

IARC (International Agency for Research on Cancer). 1979. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Some halogenated hydrocarbons. Hexachlorocyclohexane. 20: 195-241.

IARC (International Agency for Research on Cancer). 1982. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Suppl. 4: 133-135.

IARC (International Agency for Research on Cancer). 1980. An evaluation of chemicals and industrial processess associated with cancer in humans based on human and animal data: IARC Monographs Volumes 1-20. Cancer Res. 40: 1-12.

Igue, K., W.J. Farmer, W.F. Spencer and J.P. Martin. 1972. Volatility of organochlorine insecticides from soil. II. Effect of relative humidity and soil water content on dieldrin volatility. Soil Sci. Soc. Am. Proc. 36: 447-450.

Ishidate, E.M., Jr. and S. Odashima. 1977. Chromosome tests with 134 compounds on Chinese hamster cells in vitro -- A screening for chemical carcinogens. Mutat. Res. 48: 337-354.

Ito, N., I. Nagasaki, M. Arai, S. Sugehara and S. Makiura. 1973. Histologic and ultrastructural studies on the hepatocarcinogenicity of benzene hexachloride in mice. J. Natl. Cancer Inst. 51: 817-826.

Ito, N., H. Nagasaki, H. Aoe, et al. 1975. Development of hepatocellular carcinomas in rats treated with benzene hexachloride. J. Natl. Cancer Inst. 54: 801-805.

Jenssen, D. and C. Ramel. 1980. The micronucleus test as part of a short-term mutagenicity test program for the prediction of carcinogenicity evaluated by 143 agents tested. Mutat. Res. 75: 191-202.

Kan, C.A. 1978. Accumulation of organochlorine pesticides in poultry: A review. J. Agric. Food Chem. 26(5): 1051-1055.

Kan, C.A. and L.G.M.T. Tuinstra. 1976. Accumulation and excretion of certain organochlorine insecticides in broiler breeder hens. J. Agric. Food Chem. 24: 775-778.

Kanazawa, J. 1981. Measurement of the bioconcentration factors of pesticides by freshwater fish and their correlation with physicochemical properties or acute toxicities. Pestic. Sci. 12(4): 417-424.

Kaphalia, B.S. and T.D. Seth. 1981. DDT and BHC residues in some body tissues of goats, buffalo, and chickens, Lucknow, India. Pestic. Monit. J. 15(2): 103-106.

Kaphalia, B.S., M.M. Husain, T.D. Seth, A. Kumar and C.R. Krishna Murti. 1981. Organochlorine pesticide residues in some Indian wild birds. Pestic. Mon. J. 15(1): 9-13.

Kapoor, S.K., R.P. Chawla and R.L. Kalra. 1980. Contamination of bovine milk with DDT and HCH residues in relation to their usage in malaria control programme. J. Environ. Sci. Health. B15(5): 545-557.

Kar, S. and P.K. Singh. 1979. Detoxification of pesticides carbofuran and hexachlorocyclohexane by blue-green algae Nostoc muscorum and Wollea bharadwajae. Microbiol. Lett. 10(38-4): 111-114.

Karnik, A.B., K.N. Thakore, S.K. Nigam, et al. 1981. Studies on glucose-6-phosphatase, fructose-1,6-diphosphatase activity, glycogen distribution and endoplasmic reticulum changes during hexachlorocyclohexane induced hepatocarcinogenesis in pure inbred Swiss mice. Neoplasma. 28(5): 575-584.

Kastrup, E.K., Ed. 1976. Scabicides and/or Pediculocides. Facts and Comparisons, Inc., St. Louis, MO. p. 585.

Kazahevich, R.L. 1974. State of the nervous system in persons with a prolonged professional contact with hexachlorocyclohexane and products of its synthesis. Vrach. Delo. 2: 129-133.

Kellermann, G., M. Luyten-Kellermann and C.R. Shaw. 1973. Genetic variation of arylhydrocarbon hydroxylase in human lymphocytes. Am. J. Human Genet. 25: 327-331.

Kensler, T.W. and G.C. Mueller. 1978. Effects of hexachlorocyclohexane isomers on the mitogenic response of bovine lymphocytes. Biochem. Pharmacol. 27(5): 667-671.

Khera, K.S., C. Whalen, G. Trivett and G. Angers. 1979. Teratogenicity studies on pesticidal formulations of dimethoate, diuron and lindane in rats. Bull. Environ. Contam. Toxicol. 22(4-5): 522-529.

Kiraly, J., I. Szentesi, M. Ruzicska and A. Czeize. 1979. Chromosome studies in workers producing organophosphate insecticides. Arch. Environ. Contam. Toxicol. 8: 309-319.

Kitamura, S., D. Sumino and K. Hayakawa. 1970. Japan J. Publ. Health. 17: 108-112.

Koransky, W., J. Portig and G. Munch. 1963. Absorption, distribution, and elimination of α- and γ-benzene hexachloride. Arch. Exp. Pathol. Pharmacol. 244: 564-575.

Kramer, M.S., T.A. Hutchinson, S.A. Rudnick, J.M. Leventhal and A.R. Feinstein. 1980. Operational criteria for adverse drug reactions in evaluating suspected toxicity of a popular scabicide. Clin. Pharmacol. Therapeut. 27(2): 149-155.

Kraus, P., B. Gross and H.D. Kloft. 1981. The elevation of rat liver glutathione-S-transferase activity by alpha-HCH. Biochem. Pharmacol. 30: 355-361.

Krauthacker, B., T. Alebic-Kolbah, M. Kralj, B. Tkalcevic and E. Reiner. 1980. Organochlorine pesticides in blood serum of the general Yugoslav population and in occupationally exposed workers. Int. Arch. Occup. Environ. Health. 45: 217-220.

Krishnakumari, M.K. and S. Muralidhara. 1981. Acute oral toxicity of hexachlorocyclohexane and X-factor to poultry _Gallus_ _domesticus_ (chickens). Poultry Sci. 60(12): 2599-2602.

Kujawa, M., R. Engst and R. Macholz. 1977. On the metabolism of lindane. Environ. Pollut. Human Health, Proc. Internatl. Symp. (1975). p. 661-672.

Kurihara, N., K. Tanaka and M. Nakajima. 1979. Mercapturic acid formation from lindane in rats. Pestic. Biochem. Physiol. 10: 137-150.

Kutz, F.V., A.R. Yobs and S.C. Strassman. 1977. Racial stratification of organochlorine insecticide residues in human adipose tissue. J. Occup. Med. 19(9): 619-622.

Kwong, C.H. and G.C. Mueller. 1979. Effects of hexachlorocyclohexane isomers on concanavalin A 'capping' in bovine lymphocytes. Biochim. Biophys. Acta. 586(3): 501-511.

Lakkad, B.C., S.K. Nigam, A.B. Karnik, et al. 1982. Dominant-lethal study of technical-grade hexachlorocyclohexane in Swiss mice. Mutat. Res. 101: 315-320.

Lakshmanan, F.L., A. Pommer and O. Patterson. 1979. Chlorinated hydrocarbon insecticide residues in tissues of rats before and after reduction of body fat by dietary restriction. J. Agric. Food Chem. 27(4): 720-725.

Lange, M., K. Nitzche and A. Zesch. 1981. Percutaneous absorption of lindane by healthy volunteers and scabies patients. Dependency of penetration kinetics in serum upon frequency of application, time, and mode of washing. Arch. Dermatol. Res. 271(4): 387-399.

Laug, E.P. 1948. Tissue distribution of a toxicant following oral ingestion of the gamma-isomer of benzene hexachloride by rats. J. Pharmacol. Exp. Ther. 93: 277-281.

Lawlor, T., S.R. Haworth and P. Voytek. 1979. Evaluation of the genetic activity of nine chlorinated phenols, seven chlorinated benzenes and three chlorinated hexanes. Environ. Mutat. (Abstr) 1: 143.

Lehman, A.J. 1951. Chemicals in Foods: A report to the Association of Food and Drug Officials on current developments. Part II. Pesticides. Section II. Dermal Toxicity. Assoc. Food Drug Office, U.S. Quart. Bull. 15: 3-9.

Lehman, A.J. 1952a. Chemicals in foods: A report to the Association of Food and Drug Officials on current developments. Part II. Pesticides. Section IV Biochemistry. Assoc. Food and Drug Office, U.S. Quart. Bull. 16: 85-91.

Lehman, A.J. 1952b. Chemicals in foods: A report to the Association of Food and Drug Officials on current developments. Part II. Pesticides. Section V. Pathology. U.S. Assoc. Food Drug Office Quart. Bull. 16: 126-132.

Lehman, A.J. 1965. Summaries of Pesticide Toxicity. Part I. Chlorinated organic compounds. Associations of food and drug officials of the United States. Topeka, Kansas. p. 27-29.

Liu, P.T.Y. 1982. The role of genetic factors and route of administration on the metabolic disposition of lindane in mice. Dissert. Abstr. 43B: 1049.

Lowy, R., R. Albrecht, M.A. Pelissier and P. Manchon. 1977. Determination of the "no-effect levels" of two pesticides, lindane and Zineb, on the microsomal enzyme activities of rat liver. Toxicol. Appl. Pharmacol. 42: 329-338.

Macek, K.J., K.S. Buxton, S.K. Derr, J.W. Dean and S. Auter. 1976. Chronic toxicity of lindane to selected aquatic invertebrates and fishes. EPA 600/3-76-046.

Macholz, R.M., R. Knoll, H.J. Lewerenz, M. Petrzika and R. Engst. 1982a. Metabolism of α-hexachlorocyclohexane. Free metabolites in urine and organs of rats. Xenobiotica. 12(4): 227-231.

Macholz, R.M., R. Knoll, H.J. Lewerenz and R. Plass. 1982b. Biodegradation of beta-hexachlorocyclohexane. Free metabolites in rat urine and organs. Arch. Toxicol. 50: 85-88.

Mackay, D. and P.J. Leinonen. 1975. Rate of evaporation of low-solubility contaminants from water bodies to atmosphere. Environ. Sci. Technol. 9: 1178-1180.

Mackay, D. and A.W. Wolkoff. 1973. Rate of evaporation of low-solubility contaminants from water bodies to atmosphere. Environ. Sci. Technol. 7: 611-614.

Madhukar, B.V. and F. Matsumura. 1979. Comparison of induction patterns of rat hepatic microsomal mixed function oxidase by pesticides and related chemicals. Pestic. Biochem. Physiol. 11(1-3): 301-308.

Malaiyandi, M., K. Muzika and F.M. Benoit. 1982. Isomerization of γ-hexachlorocyclohexane to its α-isomer by ultraviolet light irradiation. J. Environ. Sci. Health. A17(3): 299-311.

Martin, H., Ed. 1971. Pesticide Manual, 2nd ed. British Crop Protection Council, Publ. Worcester, England. p. 464.

Masterton, W.L. and T.P. Lee. 1972. Effect of dissolved salts on water solubility of lindane. Environ. Sci. Technol. 6: 919-921.

Matsumura, F. 1975. Toxicology of Insecticides. Plenum Press, NY.

Matsumura, F. and E.G. Esaac. 1979. Degradation of pesticides by algae and aquatic microorganisms. ACS Symp. Ser. 99(Ch.22): 371-378.

Matsuoka, L.Y. 1981. Convulsions following application of gamma benzene hexachloride. J. Am. Acad. Dermatol. 5(1): 98-99.

Mes, J., D.S. Campbell, R.N. Robinson and D.J.A. Davies. 1977. Polychlorinated biphenyls and organochlorine pesticide residues in adipose tissues of Canadians. Bull. Environ. Contam. Toxicol. 17: 196-203.

Metcalf, R.L. 1981. Insect control technology. In: Kirk-Othmer Encylopedia of Chemical Technology, 3rd ed., G.J. Bushey, C.I. Eastman, H. Klingsberg, L. Spiro and M. Wainwright, Ed. John Wiley & Sons, Inc., New York. 13: 432-433.

Mikol, Y.B. and F. Decloitre. 1979. *In vitro* benzo[a]pyrene metabolism from lindane-treated rat liver: Effect of oral and acute administration and comparison with phenobarbital and methylcholanthrene pretreatment. Toxicol. Appl. Pharmacol. 47: 461-467.

Mikol, Y.B., F. Roux, F. Decloitre and E.P. Fournier. 1980. Liver-enzyme induction in lindane- and captan-treated rats. Food Cosmet. Toxicol. 18(4): 377-382.

Morgan, D.P., R.J. Roberts, A.W. Walter and E.M. Stockdale. 1980. Anemia associated with exposure to lindane. Arch. Environ. Health. 35(5): 307-310.

Müller, D., H. Klepel, R.M. Macholz, H.J. Lewerenz and R. Engst. 1981. Electroneurophysiological studies on neurotoxic effects of hexachlorocyclohexane isomers and gamma-pentachlorocyclohexene. Bull. Environ. Contam. Toxicol. 27(5): 704-706.

Munk, Z.M. and L.A. Nantel. 1977. Acute lindane poisoning with development of muscle necrosis. Can. Med. Assoc. J. 117: 1050-1051, 1054.

Muralidhara, M., K. Krishnakumari and S.K. Majumder. 1979. Effects of carriers on the oral toxicity of lindane (pesticide) (gamma-BHC) to albino rats. J. Food Sci. Technol. 16: 105-107.

Nagasaki, H., S. Tomii, T. Mega, M. Marvgami and N. Ito. 1972. Hepatocarcinogenic effect of alpha, beta, gamma, and delta isomers of benzene hexachloride in mice. Gann. 63: 805.

Nagasaki, H., H. Kawabata, P. Miyata, et al. 1975. Effect of various factors on induction of liver tumors in animals by the alpha-isomer of benzene hexachloride. Gann. 66: 185-191.

Nakajima, E., H. Shindo and N. Kurihara. 1970. Distribution of α, β, and γ-BHC-^{14}C in whole body autoradiography in mice. Radiosotope. 19: 532.

Nantel, A.J., L. Ayotte, J.-L. Benedetti, et al. 1977. A group of adults acutely poisoned by food contaminated with lindane. Acta. Pharmacol. Toxicol. 41(suppl. 2): 250.

NAS (National Academy of Sciences). 1977. Drinking Water and Health. Safe Drinking Water Committee. NAS. Washington, D.C. p. 19-62.

NAS (National Academy of Sciences). 1980. Drinking Water and Health. Safe Drinking Water Committee. NAS. Washington, D.C. p. 25-65

NCI (National Cancer Institute). 1977. Bioassay of lindane for possible carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 14. 99 p. NTIS PB-273-480.

Nichol, A.W., S. Elsbury and C.G. Rousseaux. 1981. Porphyrin accumulation in sheep bones associated with 1,2,4-trichlorobenzene. Bull. Environ. Contam. Toxicol. 27(1): 72-78.

Nigam, S.K., B.C. Lakkad, A.B. Karnik, et al. 1979. Effect of hexachlorocyclohexane feeding on testicular tissue of pure inbred mice. Bull. Environ. Contam. Toxicol. 23(4-5): 431-437.

Noack, C., J. Portig and M. Wirsching. 1975. Biodegradation of alpha-hexachlorocyclohexene: IV. The extent of degradation of single doses _in vivo_. Naunyn-Schmiedeberg's Arch. Pharmacol. 288: 57-64.

NRC (National Research Council). 1982. An assessment of the health risks of seven pesticides used for termite control. National Research Council Committee on Toxicology, Washington, DC. NTIS PB83-136374.

NRC (National Research Council). 1977. Drinking Water and Health. National Academy Press, Washington, DC. Vol. 1, p. 19-63.

Nybom, N. and B. Knutsson. 1947. Investigations on c-mitosis in _Allium cepa_. I. The cytological effect of hexachlorocyclohexane. Hereditus. 33: 220-234.

Ohisa, N. and M. Yamaguchi. 1978. Gamma BHC degradation accompanied by the growth of Clostridium rectum isolated from paddy field soil. Agric. Biol. Chem. 42(10): 1819-1823.

Ohisa, N. and M. Yamaguchi. 1979. Clostridium species and γ-BHC degradation in paddy soil. Soil Biol. Biochem. 11(6): 645-649.

Ohisa, N., M. Yamaguchi and N. Kurihara. 1980. Lindane degradation by cell-free extracts of Clostridium rectum. Arch. Microbiol. 125(3): 221-225.

Omann, G.M. and J.R. Lakowicz. 1982. Interactions of chlorinated hydrocarbon insecticides with membranes. Biochim. Biophys. Acta 684(1): 83-95.

OSHA (Occupational Safety and Health Administration). 1976. Occupational safety and health standards, Subpart 2. Toxic and hazardous substances, air contaminants. U.S. Code Fed. Regul., Title 29, part 1910.1000, p. 31: 8303.

Oshiba, K. and H. Kawakita. 1973. Interactions between toxicants and nutrition. Part C. Studies on absorption and excretion of BHC in rats. J. Food Hyg. Soc. Jpn. 14: 452-456.

Paccagnella, B., L. Prati and G. Cavazzini. 1967. Insetticidi cloroderivati organici nel tesuto adiposo di persone residenti nella provincia de Ferrara. Ann. Ig. Microbiol. 18: 17-26. (Ital.)

Palmer, A.K., A.M. Bottomley, A.N. Worden, H. Frohberg and A. Bauer. 1978a. Effect of lindane on pregnancy in the rabbit and rat. Toxicology. 9(3): 239-247.

Palmer, A.K., D.D. Cozens, E.J.F. Spicer and A.N. Worden. 1978b. Effects of lindane upon reproductive function in a 3-generation study in rats. Toxicology. 10(1): 45-54.

Parzefall, W., J. Munster and R. Schulte-Hermann. 1980. A comparative study of the effects of α-hexachlorocyclohexane and its metabolite β-pentachlorocyclohexene on growth and monooxygenase activities in rat liver. Biochem. Pharmacol. 29: 2169-2178.

Pereira, M.A., S.L. Herren, A.L. Britt and M.M. Khoury. 1982. Sex differences in enhancement of GGTase-positive foci by hexachlorocyclohexane and lindane in rat liver. Cancer Lett. (Netherlands). 15(1): 95-101.

Pernov, R. and S. Kyurkchiyev. 1974. Acute occupational poisoning by lindane. Gig. Tr. Prof. Zabol. 12: 46-47.

Plass, R., H.J. Lewerenz, R.M. Macholz and R. Engst. 1981. Effect of lindane and lindane metabolites on hepatic xenobiotic metabolizing systems. Ind. Environ. Xenobiotics, Proc. Int. Conf. 1980, p. 389-394.

Poradovsky, K., L. Rosival and A. Mesazarosova. 1977. Transplacental permeation of pesticides during normal pregnancy. Cesk. Gynekol. 42: 405-410.

Portig, J., P. Kraus, K. Stein, et al. 1979. Glutathione conjugate formation from hexachlorocyclohexane and pentachlorocyclohexene by rat liver _in vitro_. Xenobiotica. 9(6): 353-378.

Powell, G.M. 1980. Toxicity of lindane. Central Afr. J. Med. 26(7): 170.

Pramanik, A. and R.C. Hansen. 1979. Transcutaneous gamma benzene hexachloride absorption and toxicity in infants and children. Arch. Dermatol. 115(10): 1224-1225.

Prasad, J. 1981. Note on gamma-benzene hexachloride toxicity in rabbits. Ind. Vet. J. 58(6): 499-500.

Probst, G.S., R.E. McMahon, L.E. Hill, C.Z. Thompson, J.E. Epp and S.B. Neal. 1981. Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 compounds. Environ. Mutagen. 3: 11-32.

Propping, P. and W. Buselmaier. 1971. The influence of metabolism on mutagenic activity in the host-mediated assay. Arch. Toxicol. 28: 129-134.

Purchase, I.F.H., E. Longstaff, J. Ashby, et al. 1978. An evaluation of six short-term tests for detecting organic chemical carcinogenesis. Br. J. Cancer. 37: 873-903.

Purres, J. 1982. Safety of gamma-benzene hexachloride. J. Am. Acad. Dermatol. (U.S.). 7(3): 407-408.

Radaleff, R.D. and R.C. Bushland. 1960. The nature and fate of chemicals applied to soils, plants, and animals. Agric. Res. Service, USPE, Washington, D.C. 134.

Rasmussen, J.E. 1980. Lindane toxicity. Arch. Dermatol. 116: 1226.

Rasmussen, J.E. 1981. The problem of lindane. J. Am. Acad. Dermatol. 5(5): 507-516.

RCC (Research and Consulting Company, Ltd.). 1983. Lindane: Subchronic oral dosing (rat) study. EPA Pesticide Accession No. 250340.

Reuber, M.D. 1979. Carcinogenicity of lindane. Environ. Res. 19(2): 460-481.

Riedel, B. and G. Christensen. 1979. Effect of selected water toxicants and other chemicals upon adenosine triphosphatase activity _in vitro_. Bull. Environ. Contam. Toxicol. 23(3): 365-368.

Rivett, K.F., H. Chesterman, D.N. Kellett, A.J. Newman and A.N. Worden. 1978. Effects of feeding lindane to dogs for periods of up to 2 years. Toxicology. 9(3): 273-289.

Rocchi, P., P. Perocco, W. Alberghini, A. Fini and G. Prodi. 1980. Effect of pesticides on scheduled and unscheduled DNA synthesis of rat thymocytes and human lymphocytes. Arch. Toxicol. 45(2): 101-108.

Rohrborn, G. 1977. Statement on the potential mutagenicity of lindane. Hooker rebuttal submission. U.S. EPA Office of Pesticides and Toxic Substances.

Roszkowski, J. 1979. Immuno-morphological investigations on the effect of lindane, chlorphenvinphos and carbaryl on immune reactions: II. Experiments on chickens. Bull. Vet. Inst. Pulawy. 23(1-2): 25-32.

Roux, F., S. Puiseux-Dao, I. Treich and E. Fournier. 1978. Effect of lindane on mouse peritoneal macrophages. Toxicology. 11(3): 259-269.

Roux, F., I. Treich, C. Brun, B. Desoize and E. Fournier. 1979. Effect of lindane on human lymphocyte responses to phytohemagglutinin. Biochem. Pharmacol. 28(16): 2419-2426.

Roux, F., I. Treich and E. Fournier. 1980. Different levels of changes induced by the insecticide lindane in cultured C-6 glioma cells. Toxicology. 17(2): 261-264.

Sagelsdorff, P., W.K. Lutz and C. Schlatter. 1983. Covalent binding to mouse liver DNA as inconclusive mechanism of carcinogenic action of hexachlorocyclohexane isomers. EPA Pesticide Accession No. 250339.

Saleh, M.A. 1980. Isomerization of lindane by reduced hematin. Bull. Environ. Contam. Toxicol. 25: 833-836.

Sasinovich, L.M., S.M. Alekhina and I.L. Odintsova. 1974. Toxic hepatitis due to prolonged exposure to BHC. Vrach. Delo. 10: 133-135.

Sauter, E.A. and E.E. Steele. 1972. The effects of low levels of pesticide feeding on the fertility and hatchability of eggs. Poultry Sci. 51: 71-76.

Sax, K. and H.J. Sax. 1968. Possible mutagenic hazards of some food additives, beverages and insecticides. Jap. J. Genet. 43: 89-94.

Saxena, M.C. and M.K.J. Siddiqui. 1982. Pesticide pollution in India -- Organochlorine pesticides in milk of woman, buffalo, and goat. J. Dairy Sci. 65(3): 430-434.

Saxena, M.C., M.A. Siddiqui, A.K. Bhargava, T.D. Seth, C.R. Krishnamurti and D. Kutty. 1980. Role of chlorinated hydrocarbon pesticides in abortions and premature labour. Toxicology. 17: 323-331.

Saxena, M.C., M.K.J. Siddiqui, A.K. Bhargava, C.R. Krishna Murti and D. Kutty. 1981. Placental transfer of pesticides in humans. Arch. Toxicol. 48: 127-134.

Schimmel, S.E., J.M. Patrick, Jr. and J. Forester. 1977. Toxicity and bioconcentration of BHC and lindane in selected estuarine animals. Arch. Environ. Contam. Toxicol. 6: 355-363.

Schulte-Hermann, R. and W. Parzefall. 1981. Failure to discriminate initiation from promotion of liver tumors in a long-term study with the phenobarbital-type inducer alpha-hexachlorocyclohexane and the role of sustained stimulation of hepatic growth and monooxygenases. Cancer Res. 41: 4140-4146.

Seifert, J., J. Vacha and M. Seifertova. 1978. Liver growth, biosynthesis of cytidine nucleotides and level of cytochrome P-450 in rat liver after administration of a α-hexachlorocyclohexane. Chem. Biol. Interact. 20: 227-238.

Seth, T.D. and B.S. Kaphalia. 1981. 1,2,3,4,5,6-Hexachlorocyclohexane (HCH) residues in tissues of sheep. Vet. Hum. Toxicol. 23(4): 247-248.

Shahin, M.M. and R.C. Von Borstel. 1977. Mutagenic and lethal effects of α-benzene hexachloride, dibutyl phthalate and trichloroethylene in Saccharomyces cerevisae. Mutat. Res. 48: 173-180.

Sharom, M.S., J.R.W. Miles, C.R. Harris and F.L. McEwen. 1980. Persistence of 12 insecticides in water. Water Res. 14(8): 1089-1093.

Shirakowa, M. 1959. Experimental studies on the toxicity of benzene hexachloride (BHC) and dichlorodiphenylchloroethane (DDT). I. Toxicity tests of the insecticides following various administrations to laboratory animals. Kurume Med. J. 5: 65-86.

Shirasu, Y., M. Moriya, K. Kato, A. Furuhashi and T. Kada. 1976. Mutagenicity screening of pesticides in the microbial system. Mutat. Res. 40: 19-30.

Shivanandappa, T., M.Z. Krishnakumari and S.K. Majumder. 1982. Inhibition of steroidogenic activity in the adrenal cortex of rats fed benzene hexachloride (hexachlorocyclohexane). Experientia. 38(10): 1251-1253.

Shtannikov, E.V., E.V. Podzemelnikov and N. Yu Stepanova. 1978. Hygienic study of the transformation of poisonous chemicals in the process of water chlorination. Gig. Sanit. 42: 18-21.

Siddiqui, M.K.J., M.C. Saxena and C.R. Krishna Murti. 1981a. Storage of DDT and BHC in adipose tissue of Indian males. Intern. J. Environ. Anal. Chem. 10: 197-204.

Siddiqui, M.K.J., M.C. Saxena, A.K. Bhargava, T.D. Seth, C.R. Krishna Murti and D. Kutty. 1981b. Agrochemicals in maternal blood, milk, and cord blood: A source of toxicants for prenates and neonates. Environ. Res. 24: 24-32.

Sieper, H. 1972. Residues and metabolism. Toxicology of lindane. In: Lindane, E. Ulmann, Ed. Verlag K. Schillinger Publishers, Freiburg. p. 79.

Solomon, L.M., L. Fahrner and D.F. West 1977a. Gamma benzene hexachloride toxicity. Arch. Dermatol. 113: 353-357.

Solomon, L.M., D.P. West, J.F. Fitzloff and A.M. Becker. 1977b. Gamma benzene hexachloride in guinea-pig brain after topical application. J. Invest. Dermatol. 68: 310-312.

Spencer, W.F., W.J. Farmer and M.M. Cliath. 1973. Pesticide volatilization. Res. Rev. 49: 1-47.

Stanley, C.W., J.E. Barney, M.R. Helton and A.R. Yobs. 1971. Measurement of atmospheric levels of pesticides. Environ. Sci. Technol. 5: 430-435.

Starek, A. and J. Zabinski. 1970. Badania doswiadczaine nad mechanizmem wchlaniania z przewodu pokarmowego insektycydow polichlorowych. Folia Medical Cracov. 12: 419-426. (Pol.)

Stein, K., J. Portig, H. Fuhrmann, W. Koransky and G. Noack. 1980. Steric factors in the pharmacokinetics of lindane and alpha-hexachlorocyclohexane in rats. Xenobiotica. 10(1): 65-77.

Stein, K., J. Portig and G. Noack. 1981. Neuropharmacological effects of isomers of hexachlorocyclohexane. 3. An account of the convulsant activity of the gamma-isomer in rats. Neuropharmacology. 20(11): 1017-1024.

Szokolay, A., L. Rosival, J. Uhnak and A. Madari. 1977. Dynamics of benzene hexachloride (BHC) isomers and other chlorinated pesticides in the food chain and in human fat. Ecotoxicol. Environ. Safety. 1(3): 349-359.

Szymczynski, G.A. and S.M. Waliszewski. 1981a. Content of chlorinated pesticides in human semen of a random population. Int. J. Andrology. 4(6): 699-674.

Szymczynski, G.A. and S.M. Waliszewski. 1981b. Comparison of the content of chlorinated pesticide residues in human semen, testicles and fat tissues. Andrologia. 13(3): 250-252.

Taira, M.C. and L.C. San Martin de Viale. 1980. Porphyrinogen carboxylyase from chick embryo liver: In vivo effect of heptachlor and lindane. Int. J. Biochem. 12(5-6): 1033-1038.

Takahashi, W., D. Saidin, T. Takei and L. Wong. 1981. Organochlorine pesticide residues in human milk in Hawaii, 1979-1980. Bull. Environ. Contam. Toxicol. 27: 506-511.

Talanov, G.A. 1978. Pesticide movement in the organism of farm animals. In: Symposium on Environmental Transport and Transformation of Pesticides: Joint U.S.-USSR Project 02.03-31. Forms and Mechanisms by Which Pesticides and Chemicals are Transported. NTIS PB-280 714, p. 190-193.

Tanabe, S., R. Tatsukawa, M. Kawano and H. Hidaka. 1982. Global distribution and atmospheric transport of chlorinated hydrocarbons: HCH (BHC) isomers and DDT compounds in the Western Pacific, Eastern Indian and Antarctic Oceans. J. Oceanogr. Soc. Jpn. 38(3): 137-148.

Tanaka, K., N. Kurihara and M. Nakajima. 1979. Oxidative metabolism of lindane and its isomers with microsomes from rat liver and house fly abdomen. Pestic. Biochem. Physiol. 10(1): 96-103.

Telch, J. and D.A. Jarvis. 1982. Acute intoxication with lindane (gamma benzene hexachloride). Can. Med. Assoc. J. 126(6): 662-663.

Thakore, K.N., S.K. Nigam, A.B. Karnik, et al. 1981a. Early changes in serum protein and liver LDH isoenzymes in mice exposed to technical grade hexachlorocyclohexane (BHC) and their possible relationship to liver tumours. Toxicology. 19(1): 31-37.

Thakore, K.N., A.B. Karnik, S.K. Nigam, et al. 1981b. Sequential changes in lactate, isocitrate, and malate dehydrogenases in mice exposed to technical grade hexachlorocyclohexane (BHC) and their possible relationship to liver tumors. Pestic. Biochem. Physiol. 15(3): 262-266.

Thorpe, E. and A.I. Walker. 1973. The toxicology of dieldrin (HEOD). II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, beta-BHC, and gamma-BHC. Food Cosmet. Toxicol. 11: 433-442.

Tiwari, R.K., S.K. Bandyopadhyay and G.C. Chatterjee. 1982a. Protective effect of L-ascorbic acid in lindane intoxicated rats. Acta Vitaminol. Enzymol. 4(3): 215-220.

Tiwari, R.K., S.K. Bandyopadhyay, K. Chatterjee, A. Mitra, A. Banerjee and G.C. Chatterjee. 1982b. Effects of high dose application of lindane to rats and influence of L-ascorbic acid supplementation. Int. J. Vitam. Nutr. Res. 52(4): 448-455.

Tomczak, S., K. Baumann and G. Lehnert. 1981. Occupational exposure to hexachlorocyclohexane. IV. Sex hormone alterations in HCH-exposed workers. Int. Arch. Occup. Environ. Health. 48(3): 283-287.

Truhaut, R. 1954. Communication to the International Symposium on the Prevention of Cancer. Sao Paulo. 1954. Cited by FAO/WHO Expert committee on Pesticide Residues. Evaluation of some pesticide residues in food. p. 130. WHO/Food Add. 67: 32, FAO, Pl: Cp/15. Geneva, 1967.

Tullett, S.G., O. Ravie and P.E. Lake. 1982. Possible effects of gamma benzene hexachloride on developing turkey and chicken embryos. Vet. Rec. (England). 110(21): 499-500.

Turner, J.C. and V. Shanks. 1980. Absorption of some organochlorine compounds by the rat small intestine -- _in vivo_. Bull. Environ. Contam. Toxicol. 24(5): 652-655.

Tzoneva-Maneva, M.T., F. Kalianova and V. Georcieva. 1971. Influence of diazinon and lindane on the mitotic activity of the caryotype of human lymphocytes cultivated _in vitro_. Bibl. Haematol. 38: 344-347.

U.S. EPA. 1973. Unpublished report BHC-Lindane. Criteria and Evaluation Division, Office of Pesticide Programs, Washington, DC. 280 p.

U.S. EPA. 1976a. Economic Analysis of Interim Final Effluent Guidelines for the Pesticides and Agricultural Chemicals Industry -- Group II, EPA 230/1-76-065f, Washington DC, Office of Water Planning and Standards, p. 70.

U.S. EPA. 1976b. National Interim Primary Drinking Water Regulations. Office of Water Supply, Washington, DC. EPA 570/9-76-003. p. 103-108.

U.S. EPA. 1980. Ambient water quality criteria for hexachlorocyclohexane. Office of Water Regulations and Standards, Criteria and Standards Division, Washington, DC. NTIS PB81-117475.

U.S. EPA. 1985. Draft Evidence for the Registration of Pesticide Products Containing as the Active Ingredient Lindane. Office of Pesticide Programs, Washington, DC. September 30.

USITC (U.S. International Trade Commission). 1982. Imports of benzenoid chemicals and products, 1981. USITC Publ. 1272, Washington DC, U.S. Government Printing Office, p. 99.

U.S. Tariff Commission. 1951. Synthetic Organic Chemicals, U.S. Production and Sales, 1950, Report No. 173, Second Series, Washington DC, U.S. Government Printing Office, p. 127.

Vannucchi, C., S. Sivieri and M. Ceccanti. 1978. Residues of chlorinated naphthalenes, other hydrocarbons and toxic metals (Hg, Pb, Cd) in tissues of Mediterranean seagulls. Chemosphere. 6: 483-490.

Vohland, H.W., J. Portig and K. Stein. 1981. Neuropharmacological effects of isomers of hexachlorocyclohexane. 1. Protection against pentylenetetrazol-induced convulsions. Toxicol. Appl. Pharmacol. 57(3): 425-438.

von Oettingen, W.F. 1955. The halogenated hydrocarbons: Their toxicity and potential dangers. PHS Publ. 44. U.S. DHEW, U.S. Government Printing Office, p. 272-275.

Wahid, P.A. and N. Sethunathan. 1979. Sorption-desorption of α, β, and γ isomers of hexachlorocyclohexane in soils. J. Agric. Food Chem. 27(5): 1050-1053.

Wahid, P.A. and N. Sethunathan. 1980. Sorption-desorption of lindane by anaerobic and aerobic soils. J. Agric. Food Chem. 28(3): 623-625.

Wassermann, M., M. Ron, B. Bercovici, D. Wassermann, S. Cucos and A. Pines. 1982. Premature delivery and organochlorine compounds: Polychlorinated biphenyls and some organochlorine insecticides. Environ. Res. 28: 106-112.

Weil, L., G. Dure and K.E. Quentin. 1974. Solubility in water of insecticide chlorinated hydrocarbons and polychlorinated biphenyls in view of water pollution. Z. Wasser Abwasser Forsch. 7: 169-175.

Weisse, I. and M. Herbst. 1977. Carcinogenicity study of lindane in the mouse. Toxicol. 7: 233-238.

Wheeler, M. 1977. Gamma benzene hexachloride (KWELL) poisoning in a child: A case of combined cutaneous and oral administration. West. J. Med. 127(6): 518-520.

Whitehead, C.C., A.G. Downing and R.J. Pettigrew. 1972. The effect of lindane on growing hens. Br. Poultry Sci. 13: 293-295.

WHO (World Health Organization). 1984. Guidelines for Drinking Water Quality. Volume I. Recommendations. WHO, Geneva, p. 6.

Windholz, M., Ed. 1976. The Merck Index, 9th ed. Merck & Co., Inc., Rahway, NJ p. 719-720.

Wolfe, J.L. and R.J. Esher. 1980. Toxicity of carbofuran and lindane to the old-field mouse (Peromyscus polionotus) and the cotton mouse (P. gossypinus). Bull Environ. Contam. Toxicol. 24(6): 894-902.

Yamaguchi, I., F. Matsumura and A.A. Kadous. 1979. Inhibition of synaptic ATPase by heptachlorepoxide in rat brain. Pestic. Biochem. Physiol. 11: 285-293.

Zeller, F.J. and H. Hauser. 1974. Induction of polyploidy in cereal grains by lindane-based seed dressings. Experientia. 30: 345-348.

Zesch, A., K. Nitzsche and M. Lange. 1982. Demonstration of the percutaneous resorption of a lipophilic pesticide and its possible storage in the human body. Arch. Dermatol. Res. 273: 43-49.

Zimonjic, D., B. Soldatovic, M.A.N. Haidary and N. Dusin. 1981. Cytogenetical effects of some pesticides. Mutat. Res. (Abstr) 85: 285.